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LOGINID:ssspta1203mxm

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

WO 2003 091243

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 09	ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS	4	OCT 03	MATHDI removed from STN
NEWS	5	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
NEWS	6	OCT 13	New CAS Information Use Policies Effective October 17, 2005
NEWS	7	OCT 17	STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools
NEWS	8	OCT 27	Free KWIC format extended in full-text databases
NEWS	9	OCT 27	DIOGENES content streamlined
NEWS	10	OCT 27	EPFULL enhanced with additional content
NEWS	11	NOV 14	CA/CAplus - Expanded coverage of German academic research
NEWS	12	NOV 30	REGISTRY/ZREGISTRY on STN(R) enhanced with experimental spectral property data
NEWS	13	DEC 05	CASREACT(R) - Over 10 million reactions available

NEWS EXPRESS DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005.
V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
http://download.cas.org/express/v8.0-Discover/

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:13:52 ON 08 DEC 2005

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 13:14:25 ON 08 DEC 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 7 DEC 2005 HIGHEST RN 869534-51-0
DICTIONARY FILE UPDATES: 7 DEC 2005 HIGHEST RN 869534-51-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

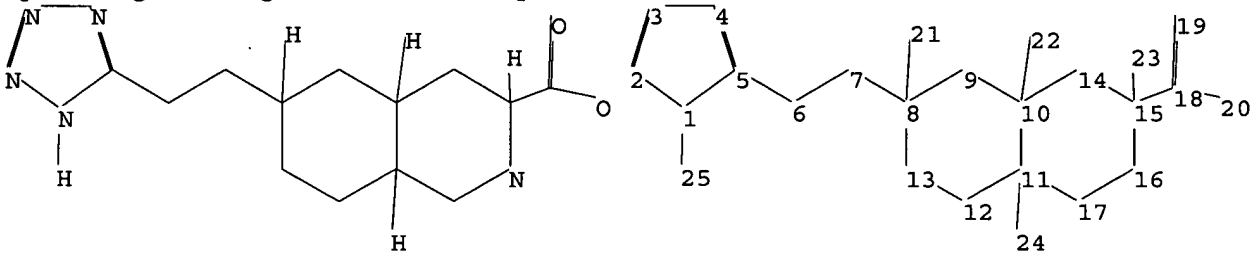
****
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10511452.str



chain nodes :
6 7 18 19 20 21 22 23 24 25
ring nodes :
1 2 3 4 5 8 9 10 11 12 13 14 15 16 17

chain bonds :
1-25 5-6 6-7 7-8 8-21 10-22 11-24 15-18 15-23 18-19 18-20
ring bonds :
1-2 1-5 2-3 3-4 4-5 8-9 8-13 9-10 10-11 10-14 11-12 11-17 12-13 14-15
15-16 16-17
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 8-9 8-13 9-10 10-11 10-14 11-12 11-17 12-13 14-15
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exact bonds :
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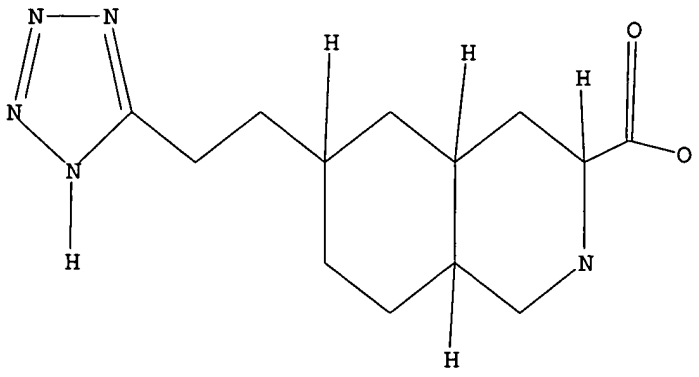
isolated ring systems :
containing 1 : 8 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 13:14:38 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 5690 TO ITERATE

100.0% PROCESSED 5690 ITERATIONS 37 ANSWERS
SEARCH TIME: 00.00.01

L2 37 SEA SSS FUL L1

=> file ca
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 161.33 161.54

FILE 'CA' ENTERED AT 13:14:41 ON 08 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Dec 2005 VOL 143 ISS 24
FILE LAST UPDATED: 1 Dec 2005 (20051201/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l2
L3           85 L2

=> s l2 and py<2003
             85 L2
       21778533 PY<2003
L4           70 L2 AND PY<2003

=> d ibib abs fhitstr 1-70
```

L4 ANSWER 1 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 140:297540 CA
TITLE: Methods of treating disorders with group I mGluR antagonists
INVENTOR(S): Bear, Mark F.; Huber, Kimberly M.; Warren, Stephen T.
PATENT ASSIGNEE(S): Brown University Research Foundation (Burf), USA; Emory University
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 114,433.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004067978	A1	20040408	US 2003-408771	20030404
US 6916821	B2	20050712		
WO 2002078745	A2	20021010	WO 2002-US10211	20020402 <--
WO 2002078745	A3	20021128		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003100539	A1	20030529	US 2002-114433	20020402
US 6890931	B2	20050510		
US 2005171067	A1	20050804	US 2004-15328	20041217

PRIORITY APPLN. INFO.:

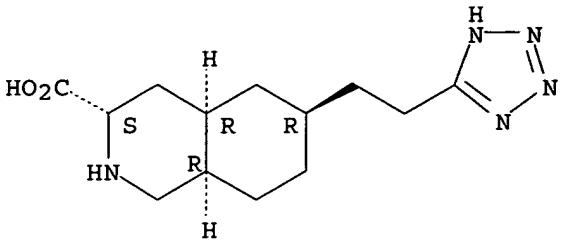
US 2001-280915P	P	20010402
US 2002-114433	A2	20020402
WO 2002-US10211	A2	20020402
US 2003-408771	A1	20030404

AB MGluR5 antagonists are used for the treatment and prevention of disorders, including Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome. The methods of the invention can be used to treat epilepsy and anxiety in a human having Fragile X syndrome, autism, mental retardation, schizophrenia and Down's Syndrome.

IT **154652-83-2**, LY293558
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treating disorders with group I mGluR antagonists)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).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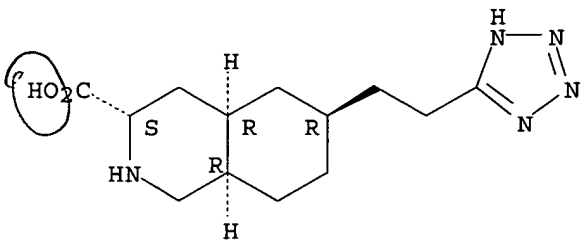
L4 ANSWER 2 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 138:117562 CA
TITLE: Effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in rats a new class of drugs for spinal anesthesia
AUTHOR(S): Von Bergen, Nicholas H.; Subieta, Alberto; Brennan, Timothy J.
CORPORATE SOURCE: University of Iowa College of Medicine, Iowa City, IA, 52242-1079, USA
SOURCE: Anesthesiology (**2002**), 97(1), 177-182
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Excitatory amino acid receptors are important for both sensory and motor function in the spinal cord. We studied the effects of intrathecal LY293558, a competitive non-N-methyl-D-aspartate excitatory amino acid receptor antagonist, on motor and sensory function in rats to determine whether drugs blocking these receptors could potentially be used as alternative agents to local anesthetics for spinal anesthesia. Rats were tested before and 15-240 min after intrathecal injection of 5 nmol (in 10 μl) LY293558. Sensory function was tested at the hind paw using withdrawal response to pin prick and withdrawal to pinch with sharp forceps. Motor performance (ambulation, placing reflex, and Rotorod time), blood pressure, and heart rate were also evaluated. Some tests were repeated the next day. Responses after LY293558 were compared to injection of 40 μl bupivacaine, 0.75%. Pin-prick responses at the forepaw, chest, abdomen, hind leg, and hind paw were also examined after intrathecal LY293558. Intrathecal LY293558 blocked both sensory and motor responses through 180 min; complete recovery was present the following day. No change in blood pressure or heart rate occurred. The effects of LY293558 were more pronounced and sustained than those of bupivacaine. Segmental blockade of the response to pin prick was present after LY293558. Drugs like LY293558 that block α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate receptors may be an alternative to local anesthetics for spinal anesthesia in humans.

IT **154652-83-2**, LY293558
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in rats a new class of drugs for spinal anesthesia)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 137:273227 CA
TITLE: Compositions and uses of mGluR5 antagonists
INVENTOR(S): Bear, Mark F.; Huber, Kimberly M.
PATENT ASSIGNEE(S): Brown University Research Foundation, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078745	A2	20021010	WO 2002-US10211	20020402 <--
WO 2002078745	A3	20021128		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2442478	AA	20021010	CA 2002-2442478	20020402 <--
EP 1392363	A2	20040303	EP 2002-757930	20020402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005500260	T2	20050106	JP 2002-577009	20020402
US 2004067978	A1	20040408	US 2003-408771	20030404
US 6916821	B2	20050712		
US 2005171067	A1	20050804	US 2004-15328	20041217

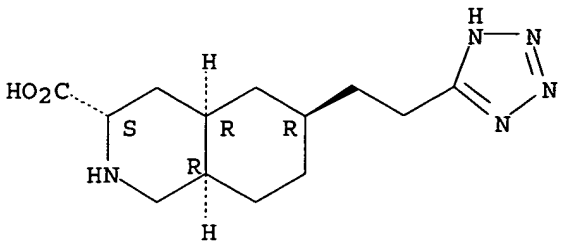
PRIORITY APPLN. INFO.:		
US 2001-280915P	P	20010402
US 2002-114433	A2	20020402
WO 2002-US10211	W	20020402
US 2003-408771	A1	20030404

AB Compns. and uses of mGluR5 antagonists for the treatment and prevention of neurol. disorders, such as Fragile X, autism, mental retardation, schizophrenia and Down's Syndrome, are disclosed.

IT **154652-83-2**, LY293558
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and uses of mGluR5 antagonists)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).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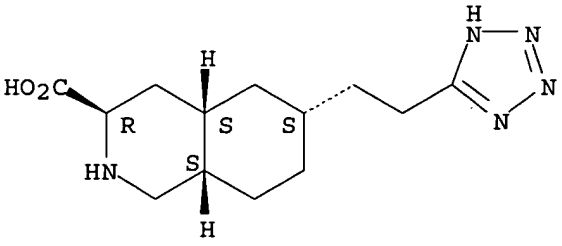
L4 ANSWER 4 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 136:95462 CA
TITLE: LY-293558(Eli Lilly & Co)
AUTHOR(S): Gilron, Ian
CORPORATE SOURCE: Departments of Anesthesiology and Pharmacology & Toxicology, Kingston General Hospital, Queen's University, Kingston, ON, K7L 2V7, Can.
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) **(2001)**, 2(9), 1273-1278
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Lilly is developing the racemic compound LY-215490, a selective and competitive AMPA antagonist, as a potential treatment for cerebral infarction, cerebrovascular ischemia, epilepsy and as an analgesic [135089], [158980], [254029], [278691]. By Jan. 2000, LY-293558 was undergoing phase II trials for pain [414000].

IT **150010-68-7**, LY-215490
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LY-215490: AMPA antagonist for analgesia)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



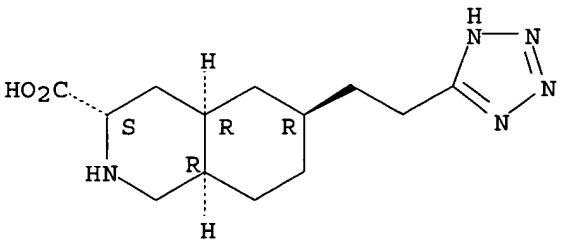
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 136:79570 CA
TITLE: Can novel AMPA and NMDA receptor antagonists induce analgesia?
AUTHOR(S): Uchikawa, Tomoyoshi; Kiuchi, Yuji; Kindscher, James; Oguchi, Katsuji; Goto, Hiroshi
CORPORATE SOURCE: Orthopedic Surgery, Showa University Fujigaoka Hospital, Yokohama, 227-8501, Japan
SOURCE: Showa University Journal of Medical Sciences (**2000**), 12(3), 235-240
CODEN: SUMSEG; ISSN: 0915-6380
PUBLISHER: Showa Medical Association and Showa University
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The glutamate receptors in the nervous system are related to nociceptive response. These receptors include the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor and the NMDA (N-methyl-D-aspartate) receptor. The purpose of this study was to investigate whether novel antagonists of these glutamate receptors could inhibit the nociceptive response in the spinal cord of male Wistar rats. Rats intrathecally (i.t.) received 0.1 to 10 pmol of Ly-293558 (a novel AMPA antagonist) and 10 to 1000 pmol of Ly-233053 (a novel NMDA antagonist) dissolved in 50 μl of physiol. saline. A 50 μl volume of 2.0% formalin solution was injected as a noxious stimulus into the hindpaw 15 min after the i.t. injections. We measured the total time the animal spent licking the hindpaw in the first 5 min (early phase) and from 10 to 30 min (late phase) after formalin injection. Controlled total licking time was 103 ± 13 s (mean ± SE) (early phase) and 151 ± 86 s (late phase). The licking time during the early phase was significantly and dose-dependently decreased with intrathecal administrations of both Ly-293558 and Ly-233053 ($p < 0.05$). However, Ly-293558 induced this effect at much lower concns. During the late phase, only the highest dose of each antagonist significantly shortened licking time. Our results indicate that these two novel AMPA and NMDA receptor antagonists when intrathecally administrated could induce antinociceptive effects during both the acute phase (peripheral sensitization) and late phase (central sensitization) of formalin-induced nociceptive stimulation without producing motor dysfunction.

IT **154652-83-2**, Ly-293558
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(can novel AMPA and NMDA receptor antagonists induce analgesia)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS

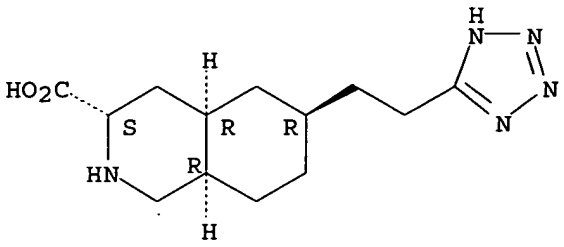
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 136:493 CA
TITLE: LY293558, an AMPA glutamate receptor antagonist, prevents and reverses levodopa-induced motor alterations in Parkinsonian rats
AUTHOR(S): Marin, C.; Jimenez, A.; Bonastre, M.; Vila, M.; Agid, Y.; Hirsch, E. C.; Tolosa, E.
CORPORATE SOURCE: Laboratori de Neurologia Experimental, Fundacio Clinic, IDIBAPS, Barcelona, 08036, Spain
SOURCE: Synapse (New York, NY, United States) (**2001**), 42(1), 40-47
CODEN: SYNAET; ISSN: 0887-4476
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate the possible involvement of glutamate AMPA receptor-mediated mechanisms in levodopa-induced motor fluctuations, we investigated the effects of LY293558, a competitive AMPA receptor antagonist, on levodopa-induced motor alterations in rats with unilateral 6-OHDA lesion. Acute and chronic administration of LY293558 was studied to evaluate the possible reversion or prevention of these levodopa effects. In the first set of expts., rats were treated with levodopa (25 mg/kg with benserazide, twice daily, i.p.) for 22 days and on day 23 LY293558 (5 mg/kg, i.p.) was administered immediately before levodopa. In the second set of expts., rats were treated daily for 22 days with levodopa and LY293558 (5 mg/kg, twice daily, i.p.). In the third set of expts., the effect of LY293558 (5 mg/kg, i.p.) administration on selective dopamine D-1 (SKF38393, 1.5 mg/kg, s.c.) and D-2 agonist (quinpirole, 0.1 mg/kg, i.p.)-induced rotational behavior after daily levodopa treatment was studied. The duration of the rotational behavior induced by chronic levodopa decreased by 30% after 22 days. Acute administration of LY293558 on day 23 reversed this effect. The group of animals that were chronically treated with levodopa and LY293558 did not show the decrease in this motor response duration. Chronic levodopa treatment attenuated the rotational response to the D-1 agonist SKF38393 and increased the response to the D-2 agonist quinpirole. LY293558 did not reverse the effect of levodopa on rotational behavior induced by the D-1 agonist but significantly reduced the rotational response to the D-2 agonist in levodopa-treated animals by 40%. Our results demonstrate that an AMPA receptor antagonist reverses and prevents levodopa-induced motor alterations in parkinsonian rats and that this effect on motor fluctuations induced by chronic levodopa is probably due to a modulation of the indirect output pathway of the basal ganglia.

IT **154652-83-2**, LY293558
RL: PAC (Pharmacological activity); BIOL (Biological study)
(LY293558 prevents and reverses levodopa-induced motor alterations in Parkinsonian rats)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

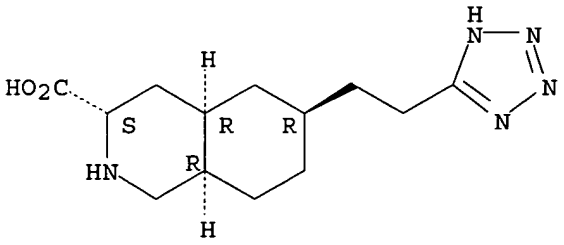
L4 ANSWER 7 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 135:170886 CA
TITLE: Analysis of weak UV-absorbing pharmaceutical drug substances using CE with condensation nucleation light-scattering detection
AUTHOR(S): Lytle, Michelle L.; Magnusson, Lars-Erik; Guo, Wei; Koropchak, John A.; Risley, Donald S.
CORPORATE SOURCE: Lilly Corporate Center, Drop 6414, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: LCGC North America (**2001**), 19(6), 624, 626, 628, 630-631
CODEN: LNACBH; ISSN: 1527-5949
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors developed new anal. methodol. to determine three pharmaceutical drug substances - LY354740, LY293558, and LY235959 - using capillary electrophoresis (CE) with condensation nucleation light-scattering detection. This CE-condensation nucleation light-scattering detection system can perform trace anal. for these drug substances, which lack sufficient UV chromophores. The authors obtained acceptable levels of precision, linearity, and limit of detection for these compds. using the CE-condensation nucleation light-scattering detection system.

IT **154652-83-2**, LY 293558
RL: ANT (Analyte); ANST (Analytical study)
(determination of pharmaceutical compds. lacking sufficient UV chromophores by
capillary electrophoresis using condensation nucleation light-scattering detection)

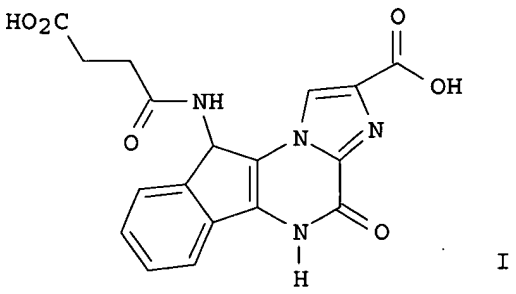
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 135:137466 CA
TITLE: Synthesis of anticonvulsive AMPA antagonists 4-Oxo-10-substituted-imidazo[1,2-a]indeno[1,2-e]pyrazin-2-carboxylic acid derivatives
AUTHOR(S): Stutzmann, J.-M.; Bohme, G. A.; Boireau, A.; Damour, D.; Debono, M. W.; Genevois-Borella, A.; Jimonet, P.; Pratt, J.; Randle, J. C. R.; Ribeill, Y.; Vuilhorgne, M.; Mignani, S.
CORPORATE SOURCE: Aventis Pharma S.A., Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, 94403, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(9), 1205-1210
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:137466
GI

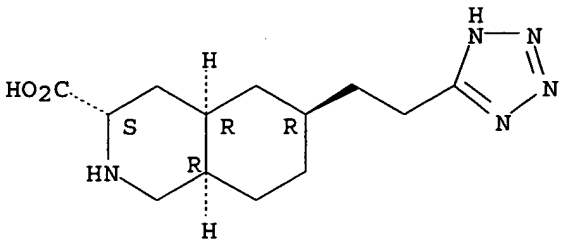


I

AB The overstimulation of excitatory amino acid receptors such as the glutamate AMPA receptor has been implicated in the physiopathogenesis of epilepsy as well as in acute and chronic neurodegenerative disorders. An original series of readily water soluble 4-oxo-10-substituted-imidazo[1,2-a]indeno[1,2-e]pyrazin-2-carboxylic acid derivs. was synthesized. The most potent derivative I exhibited nanomolar binding affinity (IC50 = 35 nM) and antagonist activity (IC50 = 6 nM) at ionotropic AMPA receptor. This compound also demonstrated potent anticonvulsant properties in MES in mice and rats with long durations of action with ED50 values in the 1-3 mg/kg dose range following i.p. and iv administration.

IT **154652-83-2**, LY-293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bioactivity of anticonvulsive imidazoindenopyrazine carboxylic acid AMPA antagonists)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



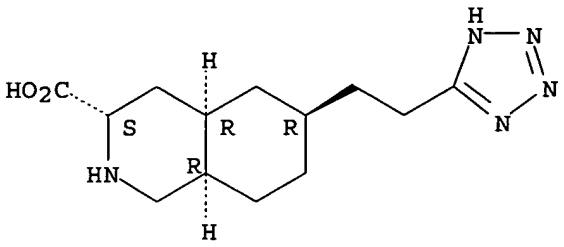
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 134:275608 CA
TITLE: Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative pain
AUTHOR(S): Gilron, Ian; Max, Mitchell B.; Lee, Gloria; Booher, Susan L.; Sang, Christine N.; Chappell, Amy S.; Dionne, Raymond A.
CORPORATE SOURCE: Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, the Department of Nursing, NIH Clinical Center, National Institutes of Health, Bethesda, MD, 20892-1258, USA
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (**2000**), 68(3), 320-327
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Previous studies suggest that 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate antagonists reduce exptl. induced pain. There have been no studies of AMPA/kainate antagonists in clin. pain. Methods: Analgesic efficacy of i.v. LY293558 (0.4 or 1.2 mg/kg) was compared with that of i.v. ketorolac tromethamine (INN, ketorolac; 30 mg) and placebo in a randomized, double-blind, parallel-group study after oral surgery (n = 70). Study drugs were administered at the onset of moderate pain; pain intensity and relief were measured for 240 min. Results: High-dose LY293558 and ketorolac tromethamine were superior to placebo ($P < .05$) for pain evoked by mouth opening and one of several measures of spontaneous pain: SPID240 ± SEM for pain evoked by mouth opening was highest for ketorolac tromethamine (151 ± 58), intermediate for high-dose LY293558 (-45 ± 35), and least for low-dose LY293558 (-151 ± 39) and placebo (-162 ± 50). High-dose LY293558 was superior to placebo at individual time points (45 to 240 min) for pain evoked by mouth opening but not for spontaneous pain. The spontaneous summed pain intensity difference over 240 min (SPID240 ± SEM) was highest for ketorolac tromethamine (303 ± 84), intermediate for high-dose LY293558 (-51 ± 40) and low-dose LY293558 (-96 ± 45), and least for placebo (-180 ± 24). LY293558 was well tolerated, with dose-dependent and reversible side effects including hazy vision in 20% of patients and sedation in 15%. Conclusions: This is the first evidence that an AMPA/kainate antagonist reduces clin. pain. Tests of evoked pain may be more sensitive to certain analgesics than those of spontaneous pain. The evaluation of evoked pain as an outcome measure in analgesic trials may identify potentially useful compds. otherwise missed if only spontaneous pain is evaluated.

IT **154652-83-2**, LY293558
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative pain in humans)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 134:95505 CA
TITLE: Decoy peptides for treatment of neurotoxicity in Alzheimer's disease caused by β amyloid peptides
INVENTOR(S): Ingram, Vernon M.; Blanchard, Barbara J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 960,188, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

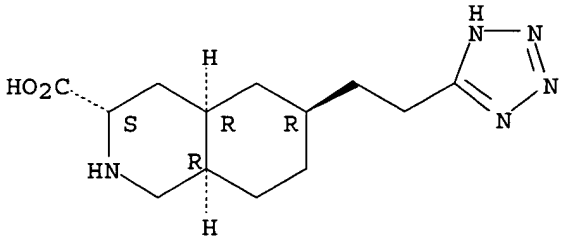
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 6172043	B1	20010109	US 1998-5215		19980109	<--
US 6942963	B1	20050913	US 2000-706574		20001103	
PRIORITY APPLN. INFO.:			US 1997-35847P	P	19970110	
			US 1997-960188	B2	19971029	
			US 1998-5215	A2	19980109	

AB The invention involves identification of a mechanism of β-amyloid peptide cytotoxicity, which enables treatment of conditions caused by β-amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can antagonize the aggregation of β-amyloid peptides and the neurotoxic effects of such aggregates. The compds. include isolated peptides which were selected for their ability to form a complex with a β-amyloid peptide, or are derived from peptides so selected. Methods for treating conditions resulting from neurotoxic β-amyloid peptide aggregates and pharmaceutical prepns. are provided. Also provided are methods for selecting addnl. compds. which can antagonize the aggregation of β-amyloid peptides and the neurotoxic effects of such aggregates.

IT **317819-68-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(decoy peptides for treatment of neurotoxicity in Alzheimer's disease caused by β amyloid peptides)

RN 317819-68-4 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrate, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● H_2O

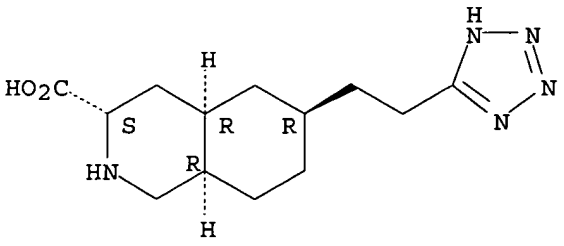
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 134:54906 CA
TITLE: Exaggerated MK-801-induced motor hyperactivity in rats with the neonatal lesion of the ventral hippocampus
AUTHOR(S): Al-Amin, H. A.; Weinberger, D. R.; Lipska, B. K.
CORPORATE SOURCE: Clinical Brain Disorders Branch, Intramural Research Programs, National Institute of Mental Health, Bethesda, MD, USA
SOURCE: Behavioural Pharmacology (**2000**), 11(3 & 4), 269-278
CODEN: BPHAEL; ISSN: 0955-8810
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neonatal lesions of the ventral hippocampus in rats produce changes in spontaneous and pharmacol. induced dopamine-dependent behaviors that emerge in early adulthood. Neural mechanisms underlying these changes may have implications for understanding the neurobiol. of schizophrenia, putatively a neurodevelopmental disorder. In this study, we evaluated the effects of MK-801 (dizocilpine), on automated measures of distance traveled and stereotypies in adult rats with neonatal (postnatal day 7) lesions, and tested the effects of haloperidol, clozapine and an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) antagonist LY293558 on the MK-801-induced behaviors. The lesioned rats showed significantly greater increases in motor activity after 0.05 and 0.1 mg/kg of MK-801 than did controls. Both haloperidol (0.1 and 0.4mg/kg) and clozapine (4 and 10mg/kg) reduced hyperlocomotion elicited by 0.2 mg/kg MK-801 in the ventral hippocampus (VH)-lesioned and sham rats. Haloperidol was more potent than clozapine in decreasing MK-801-induced stereotypy, especially in the lesioned rats. Moreover, an AMPA antagonist normalized exaggerated MK-801-induced hyperolocomotion in the lesioned rats at doses that had no effect in controls. These results demonstrate that the lesioned rats are more sensitive to MK-801 during adulthood than control rats, and that antidopaminergic drugs as well as AMPA antagonists antagonize the MK-801-induced behaviors. The neonatal lesion rat model may be useful to further our understanding of the interactions between dopamine and glutamate and their role in the pathophysiol. of schizophrenia.

IT **154652-83-2**, LY293558
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect on exaggerated MK-801-induced motor hyperactivity in rats with the neonatal lesion of the ventral hippocampus)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS

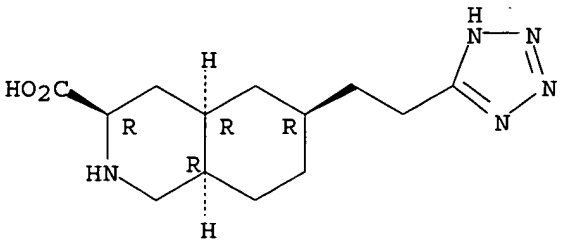
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 134:36950 CA
TITLE: Atypical antipsychotic-like effect of AMPA receptor antagonists in the rat
AUTHOR(S): Svensson, T. H.; Mathe, J. M.
CORPORATE SOURCE: Department of Physiology and Pharmacology, Section of Neuropsychopharmacology, Karolinska Institutet, Stockholm, Swed.
SOURCE: Amino Acids (2000), 19(1), 221-226
CODEN: AACIE6; ISSN: 0939-4451
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Systemic administration of two chemical different AMPA receptor antagonists, GYKI52466, 20 mg/kg, and LY326325, 18 mg/kg, given s.c., caused a selective suppression of conditioned avoidance response in the rat with preservation of escape behavior. The number of intertrial crosses was not affected and no catalepsy was observed These exptl. results indicate, in principle, an antipsychotic effect of AMPA receptor antagonists with a low liability for extrapyramidal side effects and, consequently, a pharmacol. profile consonant with atypical antipsychotic drugs.

IT **177314-99-7**, LY326325
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(atypical antipsychotic-like effect of AMPA receptor antagonists)
RN 177314-99-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aR,6R,8aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:305610 CA
TITLE: Treatment of neurological disorders with nitric oxide synthase inhibitors and excitatory amino receptor modulators
INVENTOR(S): O'Neill, Michael John
PATENT ASSIGNEE(S): Eli Lilly and Company Limited, UK
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061126	A2	20001019	WO 2000-GB1284	20000406 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

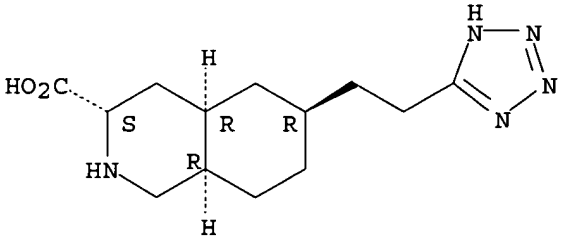
PRIORITY APPLN. INFO.: GB 1999-8175 A 19990409

AB The present invention relates to a method of treating a neurol. disorder comprising administering to a patient an effective amount of a nitric oxide synthase inhibitor in combination with an effective amount of an excitatory amino receptor modulator. Combination of 2.5 mg/kg Mk-801, i.p., and 25 mg/kg ARL17477, i.p., had a synergistic degree of neuroprotection (78%) in cerebral ischemia induced in gerbils.

IT **154652-83-2**, Ly293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of neurol. disorders with nitric oxide synthase inhibitors and excitatory amino receptor modulators)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

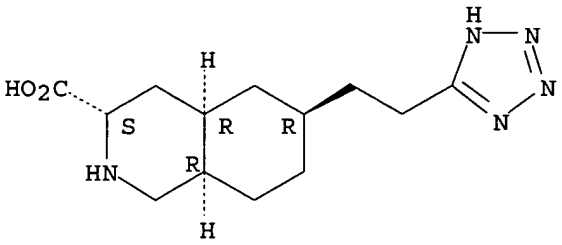


L4 ANSWER 14 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:305505 CA
TITLE: 8-Methylureido-10-amino-10-methyl-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-ones: Highly In vivo Potent and Selective AMPA Receptor Antagonists
AUTHOR(S): Jimonet, P.; Cheve, M.; Andrees Bohme, G.; Boireau, A.; Damour, D.; Williams Debono, M.; Genevois-Borella, A.; Imperato, A.; Pratt, J.; Randle, J. C. R.; Ribeill, Y.; Stutzmann, J.-M.; Vuilhorgne, M.; Mignani, S.
CORPORATE SOURCE: Aventis Pharma S.A., Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, 94403, Fr.
SOURCE: Bioorganic & Medicinal Chemistry (**2000**), 8(8), 2211-2217
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Water soluble 8-methylureido-10-amino-10-methyl-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-one 4 represents a novel class of highly potent and selective AMPA receptors antagonists with in vivo activity. The dextrorotatory isomer (+)-4 was found to display the highest affinity with an IC50 of 10 nM. It also exhibited very good anticonvulsant effects after i.p., s.c. and iv administration in mice subjected to elec. convulsions (MES) and i.p. in audiogenic seizure-e in DBA/2 mice (ED50's ≤10 mg/kg).

IT **154652-83-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(8-methylureido-10-amino-10-methyl-imidazo[1,2-a]indeno[1,2-e]pyrazine-4-ones: preparation and selective AMPA receptor antagonism)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:247292 CA
TITLE: Amyotropic lateral sclerosis treatment with a combination of riluzole and an AMPA receptor antagonist
INVENTOR(S): Bohme, Andrees; Boireau, Alain; Canton, Thierry; Pratt, Jeremy; Stutzmann, Jean-Marie
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2000054772	A1	20000921	WO 2000-FR590		20000310	<--
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
FR 2790670	A1	20000915	FR 1999-3100		19990312	<--
EP 1161238	A1	20011212	EP 2000-910920		20000310	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO						
JP 2002539162	T2	20021119	JP 2000-604848		20000310	<--
PRIORITY APPLN. INFO.:			FR 1999-3100	A	19990312	
			US 1999-129318P	P	19990414	
			WO 2000-FR590	W	20000310	

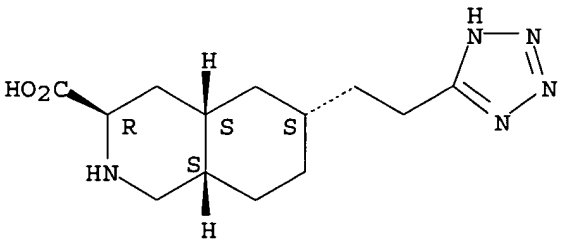
OTHER SOURCE(S): MARPAT 133:247292

AB The invention discloses the prevention and/or treatment of amyotropic lateral sclerosis with a combination of riluzole and one or several AMPA receptor antagonists, as well as combinations of these compds. and pharmaceutical compns. containing them.

IT **150010-68-7**, LY 215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(riluzole-AMPA receptor antagonist combination for treatment of amyotropic lateral sclerosis)

RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

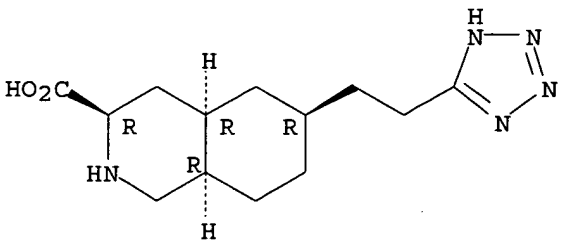
L4 ANSWER 16 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:218055 CA
TITLE: Kainate receptor-mediated activation of the AP-1 transcription factor complex in cultured rat cerebellar granule cells
AUTHOR(S): Kovacs, A. D.; Cebers, G.; Liljequist, S.
CORPORATE SOURCE: Division of Drug Dependence Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Swed.
SOURCE: Brain Research Bulletin (2000), 52(2), 127-133
CODEN: BRBUDU; ISSN: 0361-9230
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The sequence-specific DNA-binding activity of the AP-1 transcription factor complex was measured in cultured rat cerebellar granule cells by electrophoretic mobility shift assay. A low concentration of kainate (KA; 10 μM), but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; 10 μM), enhanced DNA-binding of the AP-1 transcription factor in cultures pretreated with Con A (Con A), to prevent KA receptor desensitization. In the presence of cyclothiazide (an inhibitor of AMPA receptor desensitization), KA (10 μM) caused only a slight increase of AP-1 DNA-binding, in contrast to the 3-fold enhancement produced by AMPA (10 or 30 μM) or by a higher concentration of KA (30 μM), suggesting that the effect of KA, in the presence of Con A, is mediated by activation of putative KA receptors. To confirm this, the effects of the AMPA receptor-selective, non-competitive antagonist, 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 53655; 50 μM), the mixed AMPA/KA receptor competitive antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50 μM), and the AMPA and GluR5 KA receptor competitive antagonist, (-)(3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid monohydrate (LY 326325; 100 μM), were examined on AMPA- and KA-induced AP-1 activation, resp. The authors results suggest that stimulation of native KA receptors is responsible for the observed KA-specific activation of the AP-1 transcription factor complex.

IT **177314-99-7**, LY 326325
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kainate receptor-mediated activation of AP-1 transcription factor complex in cerebellar granule cells)

RN 177314-99-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aR,6R,8aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

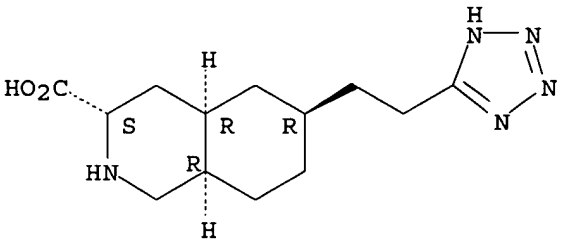
L4 ANSWER 17 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:172104 CA
TITLE: 4,10-dihydro-4-oxo-4H-imidazo[1,2-a]indeno[1,2-e]pyrazin-2-carboxylic acid derivatives: highly potent and selective AMPA receptors antagonists with in vivo activity
AUTHOR(S): Stutzmann, Jean-Marie; Bohme, Georg Andrees; Boireau, Alain; Damour, Dominique; Debono, Marc Williams; Genevois-Borella, Arielle; Imperato, Assunta; Jimonet, Patrick; Pratt, Jeremy; Randle, John C. R.; Ribeill, Yves; Vuilhorgne, Marc; Mignani, Serge
CORPORATE SOURCE: Aventis Pharma S.A., Centre de Recherche de Vitry-Alfortville, 13 quai Jules Guesde, Vitry-sur-Seine, 94403, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2000**), 10(10), 1133-1137
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel series of 2-substituted-4,5-dihydro-4-oxo-4H-imidazo[1,2-a]indeno[1,2-e]pyrazine derivs. was synthesized. One of them, 2-carboxy-8-[(methylcarbamoyl)amino]-4,10-dihydro-4-oxo-4H-imidazo[1,2-a]indeno[1,2-e]pyrazine, a highly water-soluble compound, exhibited a nanomolar affinity and demonstrated competitive antagonist properties at the ionotropic AMPA receptors. This compound also displayed potent anticonvulsant properties against elec. or sound-induced convulsions in mice after systemic administration, thus suggesting adequate brain penetration.

IT **154652-83-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(4,10-dihydro-4-oxo-4H-imidazo[1,2-a]indeno[1,2-e]pyrazine-2-carboxylic acid derivs. as highly potent and selective AMPA receptors antagonists with in vivo activity)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

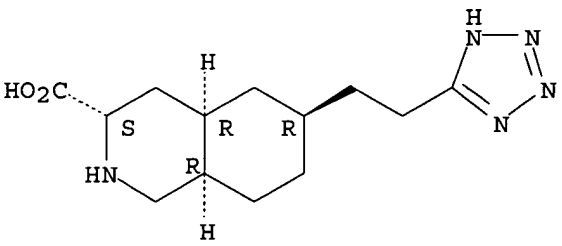
L4 ANSWER 18 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:38538 CA
TITLE: Effects of glutamate receptor antagonists on lower urinary tract function in conscious unanesthetized rats
AUTHOR(S): Nishizawa, Oamu; Igawa, Yasuhiko; Satoh, Tomoya; Yamashiro, Seiji; Sugaya, Kimio
CORPORATE SOURCE: Department of Urology, Shinshu University School of Medicine, Matsumoto City, 390, Japan
SOURCE: Advances in Experimental Medicine and Biology (**1999**), 462(Advances in Bladder Research), 275-281
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies were carried out to study the effects of the intrathecal administered glutamate receptor antagonists on the bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic spinal rats. Twenty-eight female Wistar rats with and without previous spinal cord transection were used. Before and after intrathecal administration of glutamate receptor antagonist, urodymamic parameters under isovolmetric condition of the bladder were analyzed. In normal rats, MK-801 (noncompetitive N-methyl-D-aspartate [NMDA] receptor antagonist) and LY 293558 (competitive AMPA receptor antagonist) produced a decrease in bladder contraction pressure and urethral activity with dose dependent manner. In chronic spinal rats, detrusor-sphincter dyssynergia (DSD) was developed before drug administration. MK-801 and LY 293558 partially inhibited bladder contraction pressure, and markedly depressed urethral contraction concomitant with bladder contraction. LY 293558 produced urethral relaxation concomitant with bladder contraction. Thus, in both normal rats and chronic spinal rats, two subtypes of glutamate receptors (NMDA and AMPA receptors) in the spinal cord were involved in the control of bladder and urethral activities. The AMPA receptor in the spinal cord seems to take an important role in the development of DSD.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intrathecal glutamate receptor antagonists effect on bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic spinal rats)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

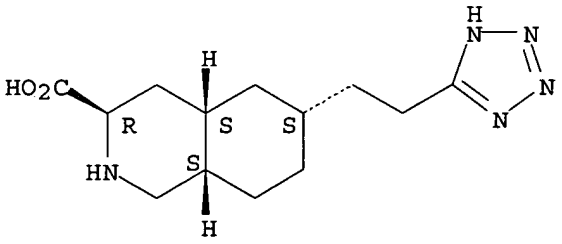
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:22497 CA
TITLE: Enantiomeric separation of an AMPA antagonist using a chirobiotic T column with HPLC and evaporative light-scattering detection
AUTHOR(S): Guisbert, Andrea L.; Sharp, V. Scott; Peterson, Jeffrey A.; Risley, Donald S.
CORPORATE SOURCE: Lilly Research Laboratories Pharmaceutical Sciences Division, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Journal of Liquid Chromatography & Related Technologies (**2000**), 23(7), 1019-1028
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A Chirobiotic T column was used for the direct separation of AMPA receptor antagonist LY293558 and the undesired enantiomer LY293559 in bulk drug substance. High performance liquid chromatog. (HPLC) separation of the enantiomers was optimized using reversed phase and hydrophilic interaction chromatog. (HILIC) by varying the organic composition of the mobile phase. Baseline resolution was achieved allowing accurate, trace level quantitation of the undesired enantiomer in the optically pure bulk material. Because the analytes lack a sufficient UV chromophore, an evaporative light-scattering detector (ELSD) was used to enhance detection. The ELSD was capable of obtaining detection limits as low as 0.1% of the undesired enantiomer. Addnl. expts. were conducted to assess the linearity, precision, and accuracy of the HPLC-ELSD system.

IT **150131-79-6**, LY293559
RL: ANT (Analyte); ANST (Analytical study)
(enantiomeric separation of AMPA antagonist by HPLC using chirobiotic T column and evaporative light-scattering detection)
RN 150131-79-6 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 133:790 CA
TITLE: New use of glutamate antagonists for the treatment of cancer
INVENTOR(S): Ikonomidou, Hrissanthi
PATENT ASSIGNEE(S): Germany
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1002535	A1	20000524	EP 1998-250380	19981028 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9964750	A1	20000515	AU 1999-64750	19991022 <--
EP 1124553	A1	20010822	EP 1999-952622	19991022 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528415	T2	20020903	JP 2000-578005	19991022 <--
EP 1586321	A1	20051019	EP 2005-12871	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 6797692	B1	20040928	US 2001-830354	20010425
US 2005054619	A1	20050310	US 2004-912159	20040806
US 2005054650	A1	20050310	US 2004-912175	20040806

PRIORITY APPLN. INFO.:

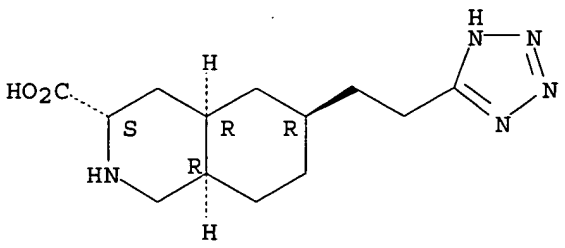
EP 1998-250380	A	19981028
EP 1999-952622	A3	19991022
WO 1999-EP8004	W	19991022
US 2001-830354	A3	20010425

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of cancer. Inhibitors of the interaction of glutamate with the AMPA, kainate, or NMDA receptor complexes are likely to be useful in treating cancer and can be formulated as pharmaceutical compns. They can be identified by appropriate screens.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for cancer treatment)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

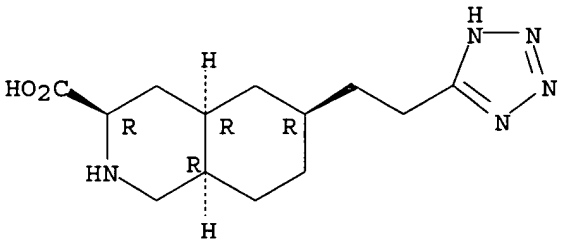
L4 ANSWER 21 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:303347 CA
TITLE: Antipsychotic-like effect of the AMPA receptor antagonist LY326325 as indicated by suppression of conditioned avoidance response in the rat
AUTHOR(S): Mathe, J. M.; Fagerquist, M. V.; Svensson, T. H.
CORPORATE SOURCE: Department of Physiology and Pharmacology, Section of Neuropsychopharmacology, Karolinska Institutet, Stockholm, Swed.
SOURCE: Journal of Neural Transmission (**1999**), 106(9-10), 1003-1009
CODEN: JNTRF3; ISSN: 1435-1463
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of LY326325, a novel AMPA receptor antagonist, on the conditioned avoidance response and catalepsy was investigated in the rat. The conditioned avoidance response is a behavioral methodol. which is considered to predict a potential antipsychotic efficacy of exptl. drugs. Catalepsy ratings were utilized to assess the putative propensity of LY325326 to induce extrapyramidal side effects. Systemic administration of LY326325, 18 mg/kg s.c., selectively suppressed the conditioned avoidance response, without effect on escape behavior or intertrial crosses. In addition, no catalepsy was observed The present and previous results support the concept of an antipsychotic effect of AMPA receptor antagonists, with a low liability for extrapyramidal side effects, i.e., pharmacol. effects consonant with an atypical antipsychotic profile.

IT **177314-99-7**, LY 326325
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antipsychotic-like effect of the AMPA receptor antagonist LY326325 in relation to suppression of the conditioned avoidance response)

RN 177314-99-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aR,6R,8aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

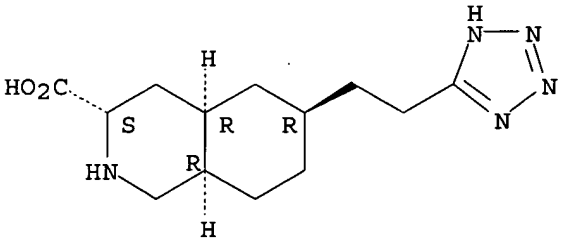
L4 ANSWER 22 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:284341 CA
TITLE: Chiral Separations of Polar Compounds by Hydrophilic Interaction Chromatography with Evaporative Light Scattering Detection
AUTHOR(S): Risley, Donald S.; Strege, Mark A.
CORPORATE SOURCE: Lilly Research Laboratories A Division of Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Analytical Chemistry (2000), 72(8), 1736-1739
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chiral sepns. of drug substances and underivatized amino acids were demonstrated in this study through the use of hydrophilic interaction chromatog. (HILIC). The polar character of the model compds. presented challenges for their anal. by traditional modes of chromatog., but through the employment of multimodal chromatog. utilizing the HILIC mechanism and cyclodextrin- or teicoplanin-derivatized stationary phases, effective resolution was achieved. The analytes lacked sufficient UV chromophores, requiring their determination by evaporative light scattering detection. HILIC was demonstrated to represent a novel technique for the facilitation of chiral chromatog. by providing an environment of solubility and retention that could not be achieved through the use of the traditional methods of reversed-phase, normal-phase, or polar organic mode.

IT **154652-83-2**
RL: ANT (Analyte); ANST (Analytical study)
(chiral sepns. of polar compds. by hydrophilic interaction chromatog. with evaporative light scattering detection)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:88184 CA
TITLE: Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex for treatment of demyelinating disorders
INVENTOR(S): Turski, Lechoslaw; Smith, Terence
PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001376	A2	20000113	WO 1999-GB2112	19990702 <--
WO 2000001376	A3	20010322		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1100504	A2	20010523	EP 1999-929545	19990702 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002519373	T2	20020702	JP 2000-557823	19990702 <--
US 2004204347	A1	20041014	US 2000-746662	20001222
US 2005130979	A1	20050616	US 2005-43219	20050126
US 2005182047	A1	20050818	US 2005-43732	20050126

PRIORITY APPLN. INFO.:

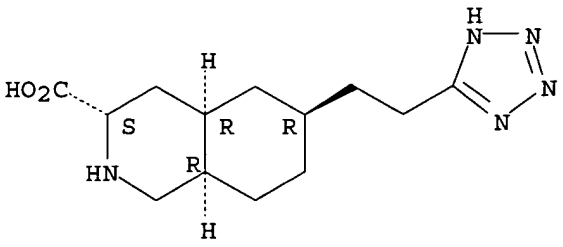
GB 1998-14380	A	19980702
GB 1998-24393	A	19981106
WO 1999-GB2112	W	19990702
US 2000-746662	B3	20001222

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of interaction of glutamate with AMPA and/or kainate receptor complex for treatment of demyelinating disorders)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



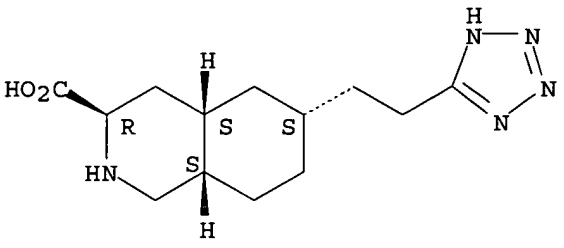
L4 ANSWER 24 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:58931 CA
TITLE: Influence of Glutamate Receptor Antagonists on Micturition in Rats with Spinal Cord Injury
AUTHOR(S): Yoshiyama, Mitsuharu; Nezu, Frank M.; Yokoyama, Osamu; Chancellor, Michael B.; de Groat, William C.
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA
SOURCE: Experimental Neurology (**1999**), 159(1), 250-257
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study was undertaken to determine if an AMPA (LY215490) or an NMDA (MK-801) glutamatergic receptor antagonist can reduce urinary tract dysfunctions related to detrusor hyperreflexia and detrusor-sphincter dyssynergia in awake, spinal cord-injured (SCI) rats. Expts. were performed on female Sprague-Dawley rats in which the spinal cord was completely transected at T8-10 level, 2-3 wk prior to performing an intravesical continuous infusion cystometrogram (CMG). Bladder volume threshold (VT) for inducing voiding and voiding efficiency (VE) were determined by measuring voided vols. and residual vols. (RV). After control CMGs were performed, cumulative i.v. doses of LY215490 (0.1, 1, and 10 mg/kg) or MK-801 (0.03, 0.3, and 3 mg/kg) were administered at 120-min intervals. Small doses of LY215490 (0.1 mg/kg) or MK-801 (0.03 and 0.3 mg/kg) did not affect any parameters. A large dose (10 mg/kg) of LY215490 decreased maximal voiding pressure (MVP) by 27% and increased RV by 119% and VT by 58% but did not decrease VE. The highest cumulative dose (3 mg/kg) of MK-801 significantly increased RV by 134% and VT by 44% and markedly decreased VE by 60% and MVP by 18%. The effects of LY215490 to reduce MVP and increase VT without changing VE suggest that an AMPA receptor antagonist might be useful in treating detrusor-sphincter dyssynergia and bladder hypertrophy after SCI. The effect of MK-801 to markedly reduce VE indicates that NMDA receptor antagonists may exacerbate neurogenic bladder dysfunction in SCI patients. (c) 1999 Academic Press.

IT **150010-68-7**, LY215490
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of glutamate receptor antagonists on micturition in rats with spinal cord injury)

RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

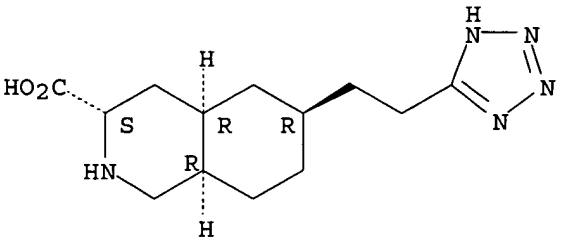
L4 ANSWER 25 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:58664 CA
TITLE: Measurement of calcium flux through ionotropic glutamate receptors using Cytostar-T scintillating microplates
AUTHOR(S): Cushing, A.; Price-Jones, M. J.; Graves, R.; Harris, A. J.; Hughes, K. T.; Bleakman, D.; Lodge, D.
CORPORATE SOURCE: Cardiff Laboratories, Amersham Pharmacia Biotech AB, Whitchurch, Cardiff, UK
SOURCE: Journal of Neuroscience Methods (**1999**), 90(1), 33-36
CODEN: JNMEDT; ISSN: 0165-0270
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human embryonic kidney cells (HEK293), expressing the human GluR4 receptor sub-unit of AMPA type non-NMDA receptors were used, in combination with Cytostar-T{™ omitted} scintillating microplates, to develop an assay system for the screening of novel compds. with potential AMPA antagonistic characteristics. Agonist dose responses were measured using the agonists: AMPA; quisqualic acid; l-glutamic acid and kainic acid (KA), and EC50 values of 40, 10, 100 and 100 μM were estimated for each of the agonists, resp. The AMPA receptor antagonists LY 293558 and GYK 152466 were tested and shown to inhibit agonist induced [45Ca] influx into the cells. An IC50 value of 600 μM was estimated for the competitive antagonist LY293558 and a value of 100 μM estimated for the non-competitive antagonist GYK 152466. The developed assay system is homogeneous, allowing increased assay precision and speed. This allows the potential for automation of the assay and it may be used for screening large nos. of novel compds.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glutamate antagonist screening by measuring calcium flux through ionotropic glutamate receptors using Cytostar-T scintillating microplates)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

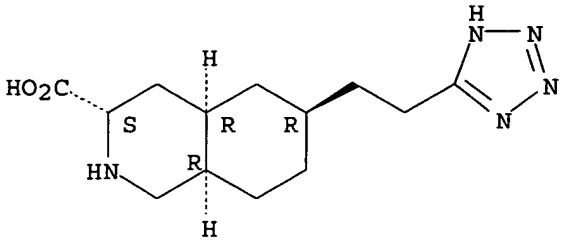
L4 ANSWER 26 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 131:335363 CA
TITLE: NMDA receptor antagonism, but not AMPA receptor antagonism attenuates induced ischemic tolerance in the gerbil hippocampus
AUTHOR(S): Bond, Ann; Lodge, David; Hicks, Caroline A.; Ward, Mark A.; O'Neill, Michael J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Company, Surrey, GU20 6PH, UK
SOURCE: European Journal of Pharmacology (**1999**), 380(2/3), 91-99
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have shown that a brief "pre-conditioning" ischemic insult reduces the hippocampal cell death caused by a subsequent more severe test insult. In the present studies, the authors have examined the effects of the non-competitive NMDA receptor antagonist ((5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, MK-801) a competitive NMDA receptor antagonist, LY202157, AMPA receptor antagonist ((3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]decahydroisoquinoline-3-carboxylic acid, LY293558), a non-competitive AMPA receptor antagonist ((-)-1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-acetyl-2,3- benzodiazepine, LY300164), and a mixed NMDA / AMPA receptor antagonist, LY246492, in a gerbil model of ischemic tolerance. Ischemic tolerance was induced by subjecting gerbils to a 2-min "pre-conditioning" ischemia (bilateral carotid occlusion) 2 days prior to a 3-min test ischemia. The effects of MK-801 (2 mg/kg i.p.), LY293558 (20 mg/kg i.p., followed by 4 + 10 mg/kg at 3 h intervals), LY300164 (4 + 10 mg/kg i.p. at 1 h intervals), LY246492 (40 mg/kg i.p., followed by 4 + 20 mg/kg i.p. at 3 h intervals) and LY202157 (30 mg/kg i.p., followed by 4 + 15 mg/kg i.p. at 2 h intervals) were then examined in this model. Initial dosing commenced 30 min prior to the 2-min "pre-conditioning" ischemia. Results indicated that a 2-min "pre-conditioning" ischemia produced ischemic tolerance in all cases. The non-competitive NMDA receptor antagonist, MK-801, produced a significant ($P < 0.01$) reduction in the induced tolerance, while the competitive NMDA receptor antagonist, LY202157, also attenuated ($P < 0.05$) the induction of tolerance. In contrast, two AMPA receptor antagonists (LY293558 and LY300164) and a mixed NMDA/AMPA receptor antagonist (LY246492) had no effect on the induction of tolerance. These results suggest that NMDA receptor activation, but not AMPA receptor activation is involved in the phenomenon of ischemic tolerance.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NMDA receptor antagonist and AMPA receptor antagonists effects in ischemic tolerance in gerbil hippocampus)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

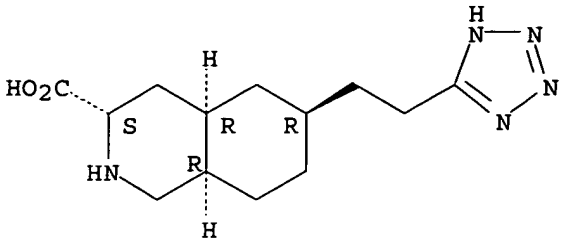
L4 ANSWER 27 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 131:317686 CA
TITLE: Synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischemia
AUTHOR(S): Hicks, C. A.; Ward, M. A.; Swettenham, J. B.; O'Neill, M. J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly & Company, Windlesham, Surrey, UK
SOURCE: European Journal of Pharmacology (**1999**), 381(2/3), 113-119
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have investigated the neuroprotective effects of combining an NMDA or AMPA receptor antagonist with a nitric oxide synthase (NOS) inhibitor in the gerbil model of global cerebral ischemia. Ischemia was induced by occlusion of the common carotid arteries for 5 min. (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801, 2.5 mg/kg i.p.) or (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]decahydroisoquinoline-3-carboxylic acid (LY293558, 20 mg/kg i.p.) and 7-nitroindazole (25 mg/kg i.p.) or N-[4-(2-{[(3-chlorophenyl)methyl]amino}ethyl) phenyl]-2-thiophenecarboximidamide dihydrochloride (ARL17477, 25 mg/kg i.p.) were administered alone or in combination (i.e., MK-801 with 7-nitroindazole or ARL17477 or LY293558 with 7-nitroindazole or ARL17477). In the present studies, both MK-801 and LY293558 provided significant degree of neuroprotection, while 7-nitroindazole and ARL17477 also provided some neuroprotection, which failed to reach significance in every case. However, the combination of MK-801 with 7-nitroindazole or ARL17477 provided 21% or 44% greater protection than the total protection or either alone. Likewise, the combination of LY293558 with 7-nitroindazole or ARL17477 provided 14.5% and 35% greater protection than total protection of either compound alone. These results indicate that several pathways contribute to ischemic cell death and combining excitatory amino antagonists and NOS inhibitors provides greater protection than either alone. Therefore, combination therapy should be considered as an approach for treating ischemic conditions.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischemia)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



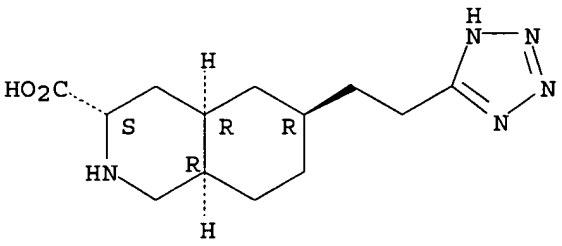
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 131:307387 CA
TITLE: Pharmacological characterization of a GluR6 kainate receptor in cultured hippocampal neurons
AUTHOR(S): Bleakman, David; Ogden, Ann-Marie; Ornstein, Paul L.; Hoo, Ken
CORPORATE SOURCE: Eli Lilly and Company, Lilly Neuroscience, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285-0510, USA
SOURCE: European Journal of Pharmacology (**1999**), 378(3), 331-337
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have examined the pharmacol. of kainate receptors in cultured hippocampal neurons (6-8 days in vitro (DIV)) from embryonic rats (E17). Cultured neurons were pre-treated with Con A to remove kainate receptor desensitization and whole-cell voltage clamp electrophysiol. employed to record inward currents in response to glutamatergic agonists and antagonists. N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor responses were blocked using MK801 (3 μM) and the 2,3-benzodiazepine, LY300168 (GYKI53655, 50 μM), resp. Inward currents were recorded in hippocampal neurons upon application of kainate and the 2S,4R isomer of 4-Me glutamic acid (SYM2081) with EC50 values of 3.4 μM and 1.6 μM, resp. (cells). The GluR5 selective agonists, LY339434 (100 μM) and (RS)-2-amino-3-(3-hydroxy-5-tert-butyl-4-isoxazolyl)propionic acid (ATPA) (100 μM), did not evoke detectable inward currents in any cell responding to kainate. LY293558 and the selective GluR5 antagonist, LY382884, had weak antagonist effects on responses evoked by either kainate or (2S,4R)-4-Me glutamate (IC50 > 300 μM). The quinoxalinedione, 2,3-dihydro-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX), blocked both kainate and (2S,4R)-4-Me glutamate-activated currents at much lower concns. (IC50 approx. 10 μM). These results provide pharmacol. evidence that ion channels comprised of GluR6 kainate receptor subunits mediate kainate receptor responses in hippocampal neurons cultured 6-8 DIV.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of a gluR6 kainate receptor in cultured hippocampal neurons in relation to ion channels)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

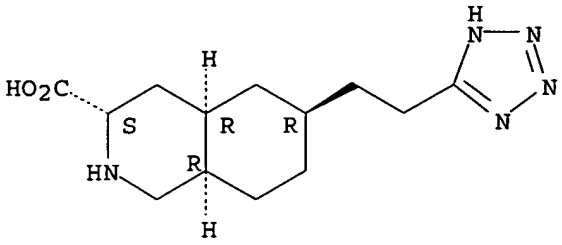
L4 ANSWER 29 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 131:179746 CA
TITLE: Systemic administration of NMDA and AMPA receptor antagonists reverses the neurochemical changes induced by nigrostriatal denervation in basal ganglia
AUTHOR(S): Vila, Miquel; Marin, Concepcio; Ruberg, Merle; Jimenez, Anna; Raisman-Vozari, Rita; Agid, Yves; Tolosa, Eduardo; Hirsch, Etienne C.
CORPORATE SOURCE: INSERM U. 289, Hopital de la Salpetriere, Paris, 75013, Fr.
SOURCE: Journal of Neurochemistry (**1999**), 73(1), 344-352
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In Parkinson's disease, nigrostriatal denervation leads to an overactivity of the subthalamic nucleus and its target areas, which is responsible of the clin. manifestations of the disease. Because the subthalamic nucleus uses glutamate as neurotransmitter and is innervated by glutamatergic fibers, pharmacol. blockade of glutamate transmission might be expected to restore the cascade of neurochem. changes induced by a dopaminergic denervation within the basal ganglia. To test this hypothesis, two types of glutamate antagonists, the NMDA receptor antagonist MK-801 and the α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor antagonist LY293558, were administered systemically, either alone or in combination with L-DOPA, in rats with a unilateral 6-hydroxydopamine lesion of the nigrostriatal dopamine pathway. The effect of treatment was assessed neurochem. by analyzing at the cellular level the functional activity of basal ganglia output structures and the subthalamic nucleus using the expression levels of the mRNAs coding for glutamic acid decarboxylase and cytochrome oxidase, resp., as mol. markers of neuronal activity. The present study shows that treatment with glutamate antagonists, and particularly with AMPA antagonists, alone or in combination with L-DOPA, reverses the overactivity of the subthalamic nucleus and its target areas induced by nigrostriatal denervation. These results furnish the neurochem. basis for the potential use of glutamate antagonists as therapeutic agents in Parkinson's disease.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(systemic administration of NMDA and AMPA receptor antagonists reverses neurochem. changes induced by nigrostriatal dopaminergic denervation in basal ganglia)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



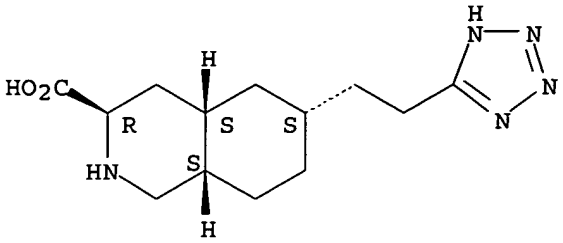
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 131:54231 CA
TITLE: Effects of N-methyl-D-aspartate (dizocilpine) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (LY215490) receptor antagonists on the voiding reflex induced by perineal stimulation in the neonatal rat
AUTHOR(S): Yoshiyama, M.; Erickson, K. A.; Erdman, S. L.; De Groat, W. C.
CORPORATE SOURCE: School of Medicine, Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Neuroscience (Oxford) (**1999**), 90(4), 1415-1420
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was undertaken to examine the role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamate receptors in the regulation of voiding reflexes induced by perineal stimulation in the neonatal rat. Four-, six- and 10-day-old awake rats were used in the expts. and perineal stimulation was applied using the tip of a 1-mL syringe to evoke voiding. Voided volume and residual volume were measured. In 10-day-old rats, LY215490 (3-10 mg/kg, i.p.), a competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor antagonist, significantly inhibited reflex voiding, increasing the residual volume 34-53-fold. A 3 mg/kg dose decreased the urine release by 55%, whereas 10 mg/kg totally suppressed the voiding reflex induced by the perineal stimulation. LY215490 (10 mg/kg, i.p.) produced similar effects in four- and six-day-old rats. Dizocilpine (1-3 mg/kg, i.p.), a non-competitive N-methyl-D-aspartate receptor antagonist, also significantly decreased the urine release (62-82%) and increased residual volume (180-230-fold). Combined administration of LY215490 (1 mg/kg, i.p.) and dizocilpine (0.3 mg/kg, i.p.) to 10-day-old rats, in doses that individually had no effect on perineal stimulation-evoked voiding, depressed voided volume by 65%. These results indicate that, in neonatal rats, glutamatergic transmission in the spinal cord has an essential role in reflex micturition induced by perineal stimulation, and that facilitatory interactions between α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamatergic mechanisms are important for voiding, as noted previously in adult rats.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glutaminergic receptor in regulation of micturition induced by perineal stimulation in development response to)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



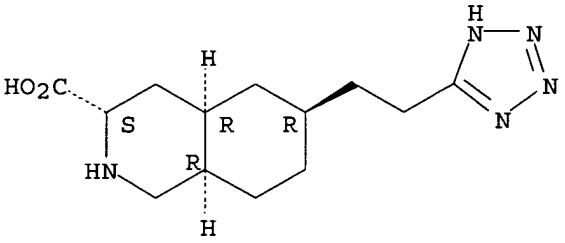
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:306464 CA
TITLE: AMPA antagonist LY293558 blocks the development, without blocking the expression, of behavioral sensitization to morphine
AUTHOR(S): Carlezon, William A., Jr.; Rasmussen, Kurt; Nestler, Eric J.
CORPORATE SOURCE: Laboratory of Molecular Psychiatry, Connecticut Mental Health Center, Yale University School of Medicine, New Haven, CT, 06508, USA
SOURCE: Synapse (New York) (**1999**), 31(4), 256-262
CODEN: SYNAET; ISSN: 0887-4476
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Morphine (3.0 mg/kg, SC) stimulates locomotor activity in rats, and this effect sensitizes with repeated intermittent treatment. We examined the ability of the AMPA antagonist LY293558, administered systemically over a range of doses (0.1-3.0 mg/kg), to alter morphine sensitization. Pretreatment with 3.0 mg/kg LY293558 attenuated the acute (session 1) locomotor-stimulating actions of morphine, whereas 1.0, 0.3, and 0.1 mg/kg were without effect. No sensitization was observed after repeated morphine treatment (3.0 mg/kg, SC, every other day for 9 days) when morphine injections were preceded by 0.3, 1.0, or 3.0 mg/kg LY293558, whereas significant sensitization was observed when morphine injections were preceded by vehicle or 0.1 mg/kg of the antagonist. When all rats were challenged with morphine (3.0 mg/kg, SC) alone on day 11, the locomotor activity of rats previously exposed to LY293558 at 3.0, 1.0, or 0.3 mg/kg-but not at 0.1 mg/kg-was significantly lower than that of rats previously given morphine preceded by vehicle. On day 13, pretreatment with 1.0 mg/kg LY293558 failed to alter preestablished morphine sensitization in rats previously pretreated with vehicle. These data indicate that LY293558 blocks the development but not the expression of morphine sensitization, confirming a role for AMPA receptors in the initiation of neurobiol. adaptations that occur with chronic morphine treatment.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA receptors role in behavioral sensitization to morphine)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



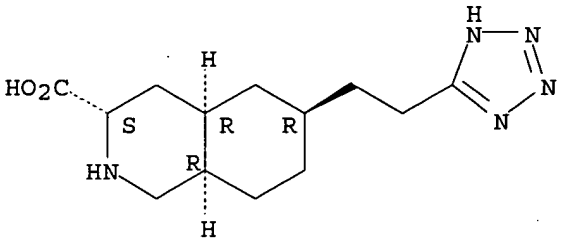
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:306451 CA
TITLE: Evaluation of glycine site antagonists of the NMDA receptor in global cerebral ischemia
AUTHOR(S): Hicks, Caroline A.; Ward, Mark A.; Ragumoorthy, Nella; Ambler, Samantha J.; Dell, Colin P.; Dobson, David; O'Neill, Michael J.
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly, Surrey, Windlesham, GU20 6PH, UK
SOURCE: Brain Research (**1999**), 819(1,2), 65-74
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present studies we have investigated the effects of a range of glycine site antagonists of the N-methyl-d-aspartate (NMDA) receptor in the gerbil model of global cerebral ischemia. The compds. tested were HA 966 (15 mg/kg), L-701324 (40 mg/kg), L-701252 (50 mg/kg), L-701273 (50 mg/kg), ACEA 1021 (25 mg/kg) and GV 150526A (40 mg/kg). All compds. were administered via the i.p. route 30 min before and again at 2 h 30 min after 5 min bilateral carotid artery occlusion (BCAO) in the gerbil. For comparison, a non-competitive NMDA antagonist, MK-801 (2 mg/kg) and an AMPA antagonist, LY293558 (20 mg/kg) were also evaluated. In the present studies L-701252, L-701324 and L-701273 provided a small degree of neuroprotection. ACEA 1021, GV 150526A and HA 966 failed to provide any neuroprotection, while MK-801 provided significant (20%) protection. In contrast LY293558 provided good (55%) neuroprotection. These results indicate that glycine site antagonists and competitive NMDA antagonists provide a small degree of neuroprotection in global cerebral ischemia. In contrast, AMPA receptor antagonists provide more robust neuroprotection in global cerebral ischemia.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison with; glycine site antagonists of NMDA receptor in global cerebral ischemia)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

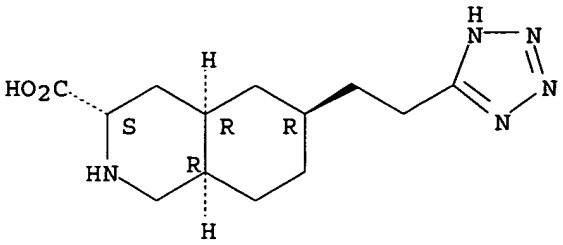
L4 ANSWER 33 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:163073 CA
TITLE: AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans
AUTHOR(S): Sang, Christine N.; Hostetter, Meredith P.; Gracely, Richard H.; Chappell, Amy S.; Schoepp, Darryle D.; Lee, Gloria; Whitcup, Scott; Caruso, Rafael; Max, Mitchell B.
CORPORATE SOURCE: NIDR/NIH Pain Research Clinic, Pain and Neurosensory Mechanisms Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA
SOURCE: Anesthesiology (**1998**), 89(5), 1060-1067
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Animal studies suggest that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-kainate (AMPA-KA) receptors are involved in pain processing. The effects of the competitive AMPA-KA antagonist LY293558 in two types of exptl. pain in human volunteers, brief pain sensations in normal skin, and mech. allodynia-pinprick hyperalgesia were studied after the injection of intradermal capsaicin. Brief i.v. infusions of the competitive AMPA-KA antagonist LY293558 were given to 25 healthy volunteers to examine acute toxicity and analgesic effects. Fifteen volunteers then entered a double-blinded, three-period crossover study. In a Phase II study, LY293558 infusions (100% maximally tolerated dose vs. 33% maximally tolerated dose vs. placebo) began 10 min after intradermal injection of 250 μg capsaicin in volar forearm. Spontaneous pain, areas of mech. allodynia and pinprick hyperalgesia, and side effects were determined every 5 min for 60 min. The median maximally tolerated dose was 1.3±0.4 (range, 0.9-2.0) mg/kg. Tests of cognitive and neurol. function were unchanged. Dose-limiting side effects were hazy vision in 95% of volunteers and sedation in 40%. There were no significant changes in elec. or warm-cool detection and pain thresholds or heat pain thresholds. LY293558 had little effect on brief pain sensations in normal skin. Both high and low doses of LY293558 significantly reduced pain intensity, pain unpleasantness, and the area in which light brush evoked pain after intradermal capsaicin. There was a trend toward a dose-response effect of LY293558 on the area in which pinprick evoked pain after intradermal capsaicin, which did not reach statistical significance. The authors infer that AMPA-KA receptor blockade reduces the spinal neuron sensitization that mediates capsaicin-evoked pain and allodynia. The low incidence of side effects at EDs of LY293558 suggests that this class of drugs may prove to be useful in clin. pain states.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



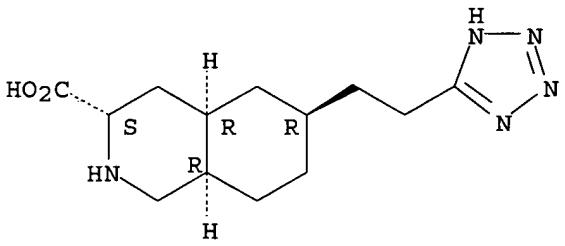
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:134099 CA
TITLE: Decahydroisoquinolines: novel competitive AMPA/kainate antagonists with neuroprotective effects in global cerebral ischemia
AUTHOR(S): O'Neill, Michael J.; Bond, Ann; Ornstein, Paul L.; Ward, Mark A.; Hicks, Caroline A.; Hoo, Ken; Bleakman, David; Lodge, David
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co. Ltd., Windlesham, GU20 6PH, UK
SOURCE: Neuropharmacology (**1998**), 37(10-11), 1211-1222
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, the activity of a series of glutamate receptor antagonists from the decahydroisoquinoline group of compds. both in vitro and in vivo, are evaluated. Compound activity at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate receptors was assessed using ligand binding to cloned iGluR2 and iGluR5 receptors and on responses evoked by AMPA and N-methyl-D-aspartate (NMDA) in the cortical wedge preparation In vivo, compds. were examined for antagonist activity electrophysiol. in the rat spinal cord preparation and in the gerbil model of global cerebral ischemia. Compds. tested were LY293558, which has been shown to protect in models of focal cerebral ischemia, LY202157 (an NMDA antagonist), LY246492 (an NMDA and AMPA receptor antagonist), LY302679, LY292025, LY307190, LY280263, LY289178, LY289525, LY294486 (AMPA/kainate antagonists) and LY382884 (an iGluR5 selective antagonist). Results obtained support a role for AMPA receptors in cerebral ischemia. LY377770 (a mixed AMPA/iGluR5 antagonist and active isomer of LY294486) demonstrated good neuroprotection with a 2-h time window and may therefore be useful in the treatment of ischemic conditions.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(decahydroisoquinoline competitive AMPA/kainate antagonists with neuroprotective effects in global cerebral ischemia)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

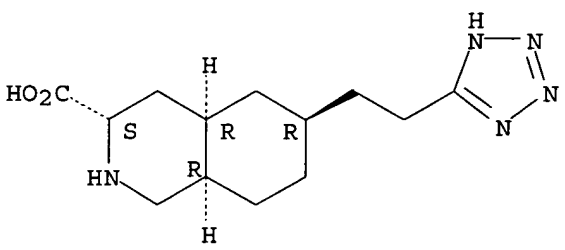
L4 ANSWER 35 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 129:170935 CA
TITLE: Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat
AUTHOR(S): Simmons, Rosa Maria A.; Li, Dominic L.; Hoo, Ken H.; Deverill, Michelle; Ornstein, Paul L.; Iyengar, Smriti
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Neuropharmacology (**1998**), 37(1), 25-36
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the roles of the AMPA and kainate subtypes of non-NMDA glutamate receptors in the processing of persistent nociceptive information, compds. with varying activities at these receptors were examined for effects on the formalin-induced paw-licking behavior in rats. The selective AMPA antagonist, LY300164 and the mixed AMPA/kainate antagonist, NBQX, were compared for their effects on formalin-induced pain behavior. NBQX (3, 10, 20 mg/kg, i.p.), caused antinociception as well as ataxia, whereas the selective AMPA antagonist, LY300164 (3,5,10 mg/kg, i.p.), did not cause antinociception at doses that did not produce ataxia. In view of the well documented distribution of kainate receptors on C fibers and of the kainate-preferring iGluR5 subtype on dorsal root ganglia (DRG), the authors tested a series of three decahydroisoquinolines with different profiles of activity between iGluR5 and AMPA receptors and all without activity on iGluR6, iGluR7 or KA2 subtypes. LY293558 (0.1, 1, 3, 5 mg/kg, i.p.), which had low micromolar affinity for both iGluR5 and 2 caused, like NBQX, both antinociceptive and ataxic effects. However, the selective iGluR5 antagonist LY382884 (5, 10, 30, 100 mg/kg, i.p.), exhibited antinociceptive actions without ataxia while the iGluR2 preferring antagonist LY302679 (5 mg/kg, i.p), caused ataxia but did not produce antinociceptive effects at that dose. These actions were stereoselective since the enantiomeric compds., LY293559 and LY302680, were ineffective in these tests. The data strongly suggest an involvement of iGluR5 in the processing of nociceptive information.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 129:131257 CA
TITLE: Treatment of neurotoxicity in Alzheimer's disease by β-amyloid peptides
INVENTOR(S): Ingram, Vernon M.; Blanchard, Barbara J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830229	A1	19980716	WO 1998-US653	19980109 <--
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2277519	AA	19980716	CA 1998-2277519	19980109 <--
EP 1015013	A1	20000705	EP 1998-902522	19980109 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

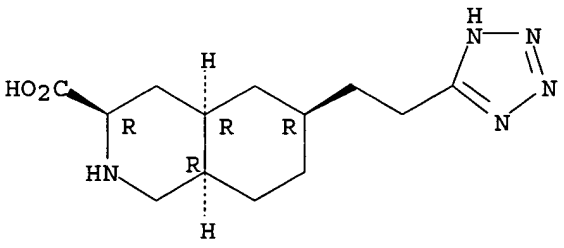
PRIORITY APPLN. INFO.:
US 1997-35847P P 19970110
US 1997-960188 A 19971029
WO 1998-US653 W 19980109

AB The invention involves identification of a mechanism of β-amyloid peptide cytotoxicity, which enables treatment of conditions caused by β-amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can antagonize the aggregation of β-amyloid peptides and the neurotoxic effects of such aggregates. The compds. include isolated peptides which were selected for their ability to form a complex with a β-amyloid peptide, or are derived from peptides so selected. Methods for treating conditions resulting from neurotoxic β-amyloid peptide aggregates and pharmaceutical prepns. are provided. Also provided are methods for selecting addnl. compds. which can antagonize the aggregation of β-amyloid peptides and the neurotoxic effects of such aggregates.

IT **177314-99-7**, LY 326325
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of neurotoxicity in Alzheimer's disease by β-amyloid peptides)

RN 177314-99-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aR,6R,8aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

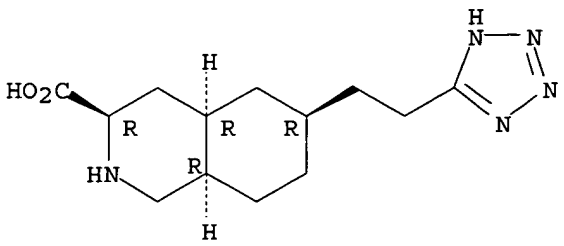
L4 ANSWER 37 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 129:62815 CA
TITLE: The putative AMPA receptor antagonist, LY326325, produces anxiolytic-like effects without altering locomotor activity in rats
AUTHOR(S): Kotlinska, Jolanta; Liljequist, Sture
CORPORATE SOURCE: Department of Clinical Neuroscience, Division of Drug Dependence Research, Karolinska Institute, Stockholm, Swed.
SOURCE: Pharmacology, Biochemistry and Behavior (**1998**), 60(1), 119-124
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anxiolytic-like effects produced by the novel, water-soluble AMPA/kainate receptor antagonist, LY326325 (3RS,4aRS,6RS,8aRS)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydro-isoquinoline-3-carboxylic acid, were examined in the elevated plus-maze and in a conflict-suppressed drinking situation. Administration of low doses (0.5, 1, 2, and 5 mg/kg; IP, -30 min) of LY326325 to Sprague-Dawley rats did not alter the percentage of entries into the open arms of the plus-maze, whereas only one dose of LY326325 (1 mg/kg) produced a slight, but significant, increase of the time spent in the open arms of the plus maze. In the conflict-suppressed drinking test, similar doses of LY326325 (2.5 and 5 mg/kg; IP, -30 min) caused a dose-dependent and significant increase of punished drinking behavior without having any significant effects on unpunished drinking. The anxiolytic-like effects of LY326325 in the plus-maze and in the anticonflict tests were observed at doses, which, by themselves, had no influence on various measures of locomotor activity, i.e., horizontal activity, forward locomotion, and corner time. Our data suggest that the putative AMPA/glutamate receptor antagonist, LY326325, produces anxiolytic-like effects similar to those of diazepam in the conflict-suppressed drinking test, but displays considerably weaker anxiety-reducing properties compared to diazepam in the elevated plus-maze.

IT **177314-99-7**, LY 326325
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(putative AMPA receptor antagonist, LY326325, produces anxiolytic-like effects without altering locomotor activity)

RN 177314-99-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aR,6R,8aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 129:23447 CA
TITLE: A method for treating tension-type headache
INVENTOR(S): Olesen, Jes; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf
PATENT ASSIGNEE(S): Den.
SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9819674	A2	19980514	WO 1997-DK502	19971104 <--
WO 9819674	A3	19980716		
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, ES, FI, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2270531	AA	19980514	CA 1997-2270531	19971104 <--
AU 9748632	A1	19980529	AU 1997-48632	19971104 <--
AU 734490	B2	20010614		
EP 1011656	A2	20000628	EP 1997-911150	19971104 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1132082	A1	20010912	EP 2000-204625	19971104 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6284794	B1	20010904	US 1999-304115	19990504 <--
AU 771266	B2	20040318	AU 2001-57775	20010802
US 2002072543	A1	20020613	US 2001-941855	20010830 <--
US 6649605	B2	20031118		
US 2004097562	A1	20040520	US 2003-702497	20031107

PRIORITY APPLN. INFO.:		
DK 1996-1243	A	19961105
US 1996-30294P	P	19961105
AU 1997-48632	A3	19971104
EP 1997-911150	A3	19971104
WO 1997-DK502	W	19971104
US 1998-85413P	P	19980514
US 1999-304115	A3	19990504
US 2001-941855	A3	20010830

AB Tension-type headache is treated by interacting with neuronal transmission in relation to pain in connection with headache in a way which prevents or decreases sensitization of second order nociceptive neurons. In particular, treatment is performed by administration of an effective amount of a substance which prevents or decreases central sensitization. Important examples of such substances are substances which interact with glutamate neurotransmission, such as glutamate receptor antagonists. Other examples are e.g. substances which interact with nitric oxide, such as nitric oxide synthase (NOS) inhibitors. According to a broader aspect of the invention, tension-type headache is treated by administration of substances which are effective in preventing or decreasing pain in connection with tension-type headache. An addnl. aspect of the invention

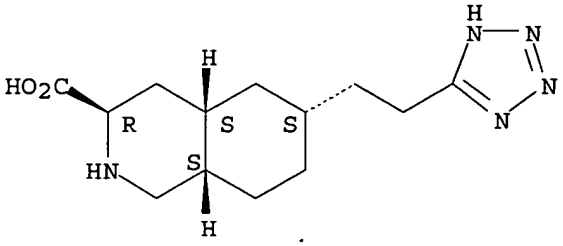
relates to treatment of tension-type headache by administration of substances which substantially inhibit the activity of NOS. Evidence for central sensitization in chronic myofascial pain, as well as mechanisms of spontaneous tension-type headaches, are also described. Gabapentin and dextromethorphan had a prophylactic effect on chronic tension-type headaches.

IT **150010-68-7**, LY 215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tension-type headache treatment)

RN 150010-68-7 CA

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



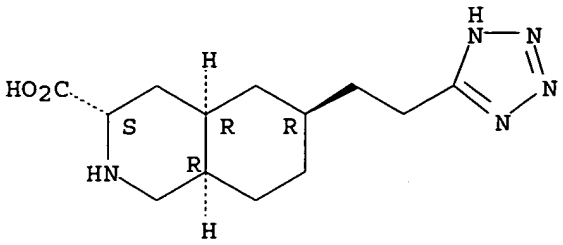
L4 ANSWER 39 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 129:12636 CA
TITLE: Effects of AMPA receptor antagonists on dopamine-mediated behaviors in mice
AUTHOR(S): Vanover, Kimberly E.
CORPORATE SOURCE: Department of Pharmacology, CoCensys, Inc., Irvine, CA, 92618, USA
SOURCE: Psychopharmacology (Berlin) (**1998**), 136(2), 123-131
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Current data indicate that dopaminergic and glutamatergic neurotransmitter systems interact. The role of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor subtypes in modulating dopamine neurotransmission, however, remains unclear. The noncompetitive AMPA antagonists, GYKI 52466 (5-40 mg/kg) and LY300164 (1-6 mg/kg), and the competitive AMPA antagonists, LY326325 (5-80 mg/kg) and NBQX (10-80 mg/kg), were compared to the dopamine antagonist, haloperidol (0.03-1.0 mg/kg), for their ability to inhibit dopamine-mediated behaviors after IP administration in mice. The behavioral paradigms included amphetamine- or dizocilpine-induced hyperactivity, amphetamine-induced stereotyped sniffing, and apomorphine-induced climbing and stereotyped sniffing. All four AMPA antagonists and haloperidol attenuated amphetamine-and dizocilpine-induced hyperactivity and decreased spontaneous locomotion. Haloperidol and GYKI 52466 were more potent against amphetamine than against dizocilpine. In contrast, LY326325 was more potent against dizocilpine than against amphetamine. The hyperactivity decreases by LY300164 and NBQX were most likely due to non-specific effects on motor behavior. The AMPA antagonists and haloperidol also attenuated amphetamine- induced stereotypy. Unlike haloperidol, however, GYKI 52466, LY300164, and NBQX failed to attenuate apomorphine-induced climbing and stereotyped sniffing. LY326325, attenuated apomorphine-induced stereotypy, but not climbing. These results indicate that AMPA receptor antagonists can attenuate the behavioral effects of drugs, such as amphetamine and dizocilpine, that increase dopamine neurotransmission. However, the behavioral effects of the direct dopamine agonist apomorphine are not consistently attenuated by AMPA antagonists. The competitive AMPA receptor antagonist LY326325 appears to have a profile distinct from both haloperidol and the other AMPA antagonists tested.

IT **154652-83-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA receptor antagonists effects on dopamine-mediated behaviors in mice)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



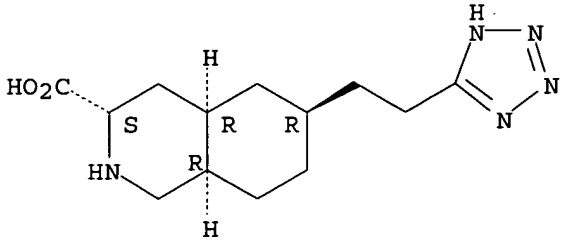
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 128:279155 CA
TITLE: The synaptic activation of the GluR5 subtype of kainate receptor in area CA3 of the rat hippocampus
AUTHOR(S): Vignes, M.; Bleakman, D.; Lodge, D.; Collingridge, G. L.
CORPORATE SOURCE: Department of Anatomy, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Neuropharmacology (**1998**), Volume Date 1997, 36(11/12), 1477-1481
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two new compds. (LY293558 and LY294486), that antagonize homomeric human GluR5 receptors, were examined against responses mediated by kainate receptors in the CA3 region of rat hippocampal slices. Both compds. (applied at a concentration of 10 μM) antagonized reversibly currents induced by 200 nM kainate. They also antagonized reversibly the synaptic activation of kainate receptors, evoked by high-frequency stimulation of mossy fibers, in the presence of NMDA and AMPA receptor antagonists. These results show that GluR5 subunits are likely to contribute to a kainate receptor on CA3 neurons that mediates responses to both kainate and synaptically-released L-glutamate.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synaptic activation of the GluR5 subtype of kainate receptor in area CA3 of the rat hippocampus)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

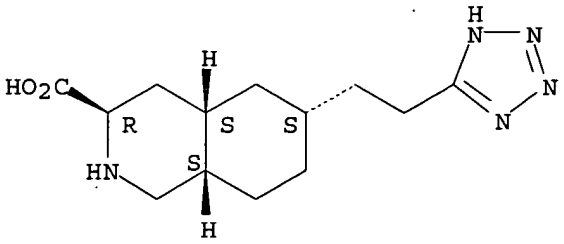
L4 ANSWER 41 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 128:212404 CA
TITLE: The separation of enantiomers by counter current capillary electrophoresis using the macrocyclic antibiotic A82846B
AUTHOR(S): Reilly, John; Risley, Donald S.
CORPORATE SOURCE: Lilly Res. Centre Ltd., Eli Lilly and Co., Windlesham/Surrey, GU20 6PH, UK
SOURCE: LC-GC (**1998**), 16(2), 170, 172, 174, 176, 178
CODEN: LCGCE7; ISSN: 0888-9090
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors evaluated the macrocyclic antibiotic A82846B as a chiral selector by countercurrent capillary electrophoresis using three dansyl amino acids, three antiinflammatory compds., and the 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid antagonist LY215490 as the test analytes. They evaluated the chiral selectivity of A82846B as a function of the run buffer pH and antibiotic concentration After optimizing variations of these parameters, the macrocyclic antibiotic A82846B provided high resolns. of all the enantiomers for the compds. tested. The detection and enantiosepn. of LY215490, a compound lacking an adequate UV chromophore, demonstrated the practicality of the counter-current process using A82846B, a chiral selector possessing a strong UV chromophore.

IT **150010-68-7**, LY 215490
RL: ANT (Analyte); PEP (Physical, engineering or chemical process); ANST (Analytical study); PROC (Process)
(separation of enantiomers by counter current capillary electrophoresis using macrocyclic antibiotic A82846B)

RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

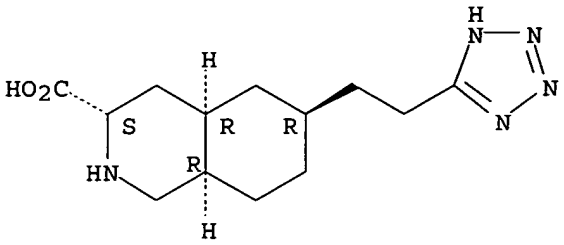
L4 ANSWER 42 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 128:149482 CA
TITLE: The competitive α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist LY293558 attenuates and reverses analgesic tolerance to morphine but not to delta or kappa opioids
AUTHOR(S): Kest, Benjamin; McLemore, Gabrielle; Kao, Bernard; Inturrisi, Charles E.
CORPORATE SOURCE: Department of Pharmacology, Cornell University Medical College, New York, NY, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1997**), 283(3), 1249-1255
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antagonists of the NMDA type of excitatory amino acid (EAA) receptor attenuate or reverse the development of tolerance to the analgesic effects of the μ opioid agonist morphine, the δ-1 opioid agonist DPDPE but not the κ-1 agonist U50488H or the κ-3 agonist naloxone benzoylhydrazone. The role of the AMPA subtype of EAA receptor in analgesic tolerance was examined using LY293558, a selective competitive antagonist that is active after systemic administration. Administration of morphine, DPDPE, or U50488H three times daily for 3 days according to an escalating dosing schedule resulted in analgesic tolerance as indicated by an increase in analgesic ED50 values using the tail-flick test in mice. Analgesic tolerance was attenuated when mice received a continuous s.c. infusion of LY293558 at doses of 30, 45 or 60 mg/kg/24 h via an osmotic pump concurrent with the morphine treatment. Continuous s.c. infusion of LY293558 (45 mg/kg/24 h) also reversed established morphine tolerance. In contrast, continuous s.c. infusion of the highest dose of LY293558 (60 mg/kg/24 h) was ineffective in preventing the development of analgesic tolerance to DPDPE or U50488H. Continuous s.c. infusion of LY293558 (60 mg/kg/24 h) for 3 days protected mice from generalized convulsions produced by the selective AMPA agonist ATPA, indicating that the dosage of LY293558 that attenuated morphine tolerance was effective as an antagonist at AMPA receptors. These results demonstrate that AMPA receptors may play a role in the development and maintenance of morphine, but not DPDPE or U50488H, analgesic tolerance.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(competitive AMPA receptor antagonist LY293558 attenuation and reversal of analgesic tolerance to μ opioid but not to δ or κ opioids)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



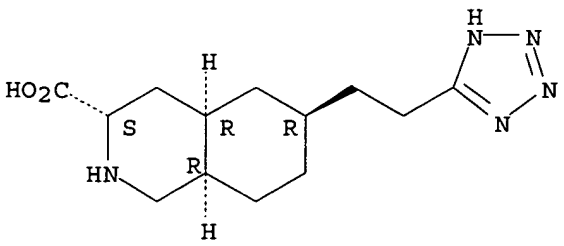
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 43 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 128:123724 CA
TITLE: The effects of LY293558, an AMPA receptor antagonist, on acute and chronic morphine dependence
AUTHOR(S): McLemore, Gabrielle L.; Kest, Benjamin; Inturrisi, Charles E.
CORPORATE SOURCE: York Avenue, LC-524, Department of Pharmacology, Cornell University Medical College, New York, NY 10021, 1300, USA
SOURCE: Brain Research (**1997**), 778(1), 120-126
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In rodents, noncompetitive and competitive NMDA receptor antagonists have been shown to attenuate and, in some cases, reverse tolerance to the analgesic effects of morphine. However, the ability of these same excitatory amino acid (EAA) receptor antagonists to modulate morphine dependence is controversial, and very little is known about the role of AMPA receptors in morphine dependence. LY293558, a novel, systemically active, competitive AMPA receptor antagonist and the NMDA receptor antagonists, MK-801 and/or LY235959, were evaluated in tolerant or dependent CD-1 mice. In mice rendered tolerant by morphine injection or pellet implantation, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or MK-801 (1 mg/kg per 24 h) attenuated the development of tolerance. Neither LY293558 nor MK-801 produced analgesia or altered the ED50 value of morphine. Continuous s.c. infusion of LY293558 (60 mg/kg per 24 h), MK-801 (1 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) attenuated the development of acute (3 h) morphine dependence (i.e., decreased naloxone-precipitated withdrawal jumping). In contrast, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) did not significantly attenuate the development of chronic dependence produced by morphine pellet implantation. These data indicate that the development of morphine tolerance is more sensitive to modulation by EAA receptor antagonists than is the development of morphine dependence as assessed by naloxone-precipitated withdrawal jumping.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of AMPA and NMDA receptor antagonists on acute and chronic morphine dependence)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

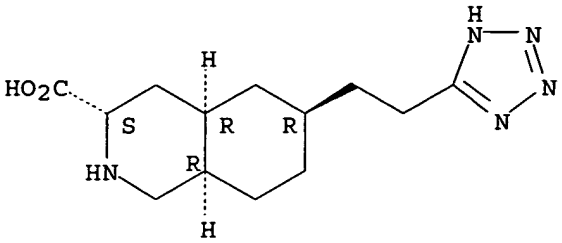
L4 ANSWER 44 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 127:199905 CA
TITLE: Effects of Ca2+ and Na+ channel inhibitors in vitro and in global cerebral ischemia in vivo
AUTHOR(S): O'Neill, Michael J.; Bath, Catherine P.; Dell, Colin P.; Hicks, Caroline A.; Gilmore, Jeremy; Ambler, Samantha J.; Ward, Mark A.; Bleakman, David
CORPORATE SOURCE: Eli Lilly and Company Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham Surrey, GU20 6PH, UK
SOURCE: European Journal of Pharmacology (**1997**), 332(2), 121-131
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study we have examined the effects of the small organic mols.: NNC 09-0026 ((-)-trans-1-butyl-4-(4-dimethylaminophenyl)-3-[(4-trifluoromethyl-phenoxy)methyl] piperidine dihydrochloride); SB 201823-A (4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentyl piperidine hydrochloride); NS 649 (2-amino-1-(2,5-dimethoxyphenyl)-5-trifluoromethyl benzimidazole); CNS 1237 (N-acenaphthyl-N'-4-methoxynaphth-1-yl guanidine) and riluzole on human ω-conotoxin sensitive N-type voltage-dependent Ca2+ channel currents (ICa) expressed in HEK293 cells, on Na+ channel currents (INa) in acutely isolated cerebellar Purkinje neurons in vitro and in the gerbil model of global cerebral ischemia in vivo. Estimated IC50 values for steady-state inhibition of ICa were as follows; NNC 09-0026, 1.1 μM; CNS 1237, 4.2 μM; SB 201823-A, 11.2 μM; NS 649, 45.7 μM and riluzole, 233 μM. Estimated IC50 values for steady-state inhibition of Na+ channel currents were as follows: NNC 09-0026, 9.8 μM; CNS 1237, 2.5 μM; SB 201823-A, 4.6 μM; NS 649, 36.7 μM and riluzole, 9.4 μM. In the gerbil model of global cerebral ischemia the number of viable cells (mean±S.E.M.) per 1 mm of the CA1 was 215±7 (sham operated), 10±2 (ischemic control), 44±15 (NNC 09-0026 30 mg/kg i.p.), 49±19 (CNS 1237 30 mg/kg i.p.), 11±2 (SB 201823-A 10 mg/kg i.p.), 17±4 (NS 649 50 mg/kg i.p.) and 48±18 (riluzole 10 mg/kg i.p.). Thus NNC 09-0026, CNS 1237 and riluzole provided significant neuroprotection when administered prior to occlusion while SB 201823-A and NS 649 failed to protect. These results indicate that the Ca2+ channel antagonists studied not only inhibited human N-type voltage-dependent Ca2+ channels but were also effective blockers of rat Na+ channels. Both NNC 09-0026 and CNS 1237 showed good activity at both Ca2+ and Na+ channels and this may contribute to the observed neuroprotection.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison with; effects of Ca2+ and Na+ channel inhibitors in vitro and in global cerebral ischemia in vivo)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



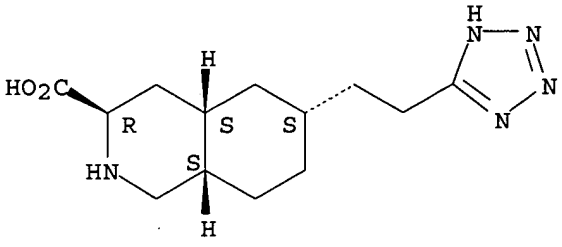
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 45 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 127:170899 CA
TITLE: (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl) ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558) and its racemate (LY215490): a selective and competitive AMPA/kainate receptor antagonist
AUTHOR(S): Lodge, David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Res. Centre Ltd., Eli Lilly & Co., Surrey, GU20 6PH, UK
SOURCE: Excitatory Amino Acids: Clinical Results with Antagonists (**1997**), 81-87, 129-152.
Editor(s): Herrling, P. L. Academic: London, UK.
CODEN: 64UIAO
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with over 550 refs. During the structure-activity development of series of decahydroisoquinoline-based N-methyl-D-aspartate (NMDA) antagonists, some compds. in the series showed activity at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Of these, (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisouinoline-3-carboxylic acid (LY293558) (Fig. 1) was one of the most potent and selective for AMPA receptors in vitro and in vivo. LY215490 is the racemic mixture LY293558 is centrally active following parenteral administration in animals, with no NMDA receptor antagonist activity at in vivo doses which block AMPA receptors, and a pharmacol. consistent with effects of other known AMPA antagonists. LY293558 possesses neuroprotectant activity against AMPA- and ischemia-induced neuronal injury in multiple animal models including focal ischemia in the rat and cat, and spinal ischemia in the rabbit. Thus, LY293558 may have clin. utility as a neuroprotectant in patients subjected to an ischemic neuronal event that involves glutamate excitotoxicity.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LY293558 and its racemate LY215490: selective and competitive AMPA/kainate receptor antagonists)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

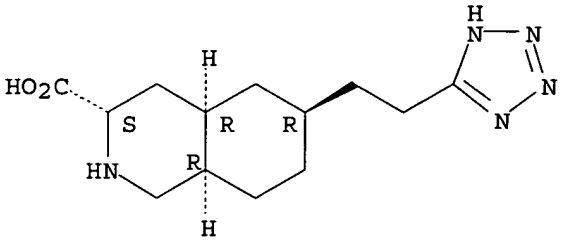


L4 ANSWER 46 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 127:117055 CA
TITLE: Homology modeling of the AMPA receptor: a quantitative predictive tool for the design of novel antagonists
AUTHOR(S): Hesson, David P.; Sturgess, Michael A.
CORPORATE SOURCE: Symphony Pharmaceuticals Inc., Frazer, PA, 19355, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1997**), 7(11), 1437-1442
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A homol. model of the AMPA receptor has been employed to construct a QSAR model of the AMPA receptor antagonist binding site.

IT **154652-83-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(QSAR of AMPA receptor antagonists)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 47 OF 70 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 127:90115 CA

TITLE: Structure-activity studies of aryl-spaced decahydroisoquinoline-3-carboxylic acid AMPA receptor antagonists

AUTHOR(S): Bleisch, Thomas J.; Ornstein, Paul L.; Allen, Nancy K.; Wright, Rebecca A.; Lodge, David; Schoepp, Darryle D.

CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporation Center, Indianapolis, IN, 46285, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (**1997**), 7(9), 1161-1166
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

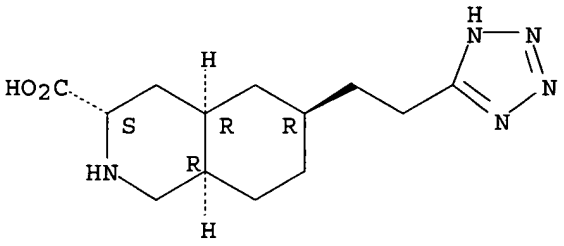
AB We report the synthesis and structure-activity studies of a series of decahydroisoquinoline AMPA antagonists where the distal acid is joined to the bicyclic ring nucleus with a spacer that contains an aromatic ring. These Ph and thienyl substituted compds. are characterized as relatively potent AMPA antagonists.

IT **154652-83-2P**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity studies of aryl-spaced decahydroisoquinoline-3-carboxylic acid AMPA receptor antagonists)

RN 154652-83-2 CA

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

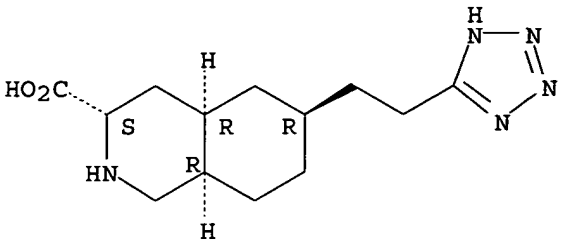
L4 ANSWER 48 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:288414 CA
TITLE: L-trans-Pyrrolidine-2,4-dicarboxylic acid-evoked striatal glutamate levels are attenuated by calcium reduction, tetrodotoxin, and glutamate receptor blockade
AUTHOR(S): Rawls, Scott M.; Mcginty, Jacqueline F.
CORPORATE SOURCE: Department of Anatomy and Cell Biology, East Carolina University School of Medicine, Greenville, NC, 27858-4354, USA
SOURCE: Journal of Neurochemistry (**1997**), 68(4), 1553-1563
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB L-trans-Pyrrolidine-2,4-dicarboxylic acid (L-trans-PDC) reverses plasma membrane glutamate transporters and elevates extracellular glutamate levels in vivo. We investigated the possibility that L-trans-PDC-stimulated glutamate levels are mediated partially by increases in transsynaptic activity. Therefore, the degree to which L-trans-PDC-evoked glutamate levels depend on calcium, sodium-channel activation, and glutamate-receptor activation was investigated by infusing via reverse microdialysis (a) 0.1 mM calcium, (b) 1 μM tetrodotoxin, a selective blocker of voltage-dependent sodium channels, (c) R(-)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), a selective NMDA-receptor antagonist, or (d) LY293558, a selective α-amino-3-hydroxy-5-methylisoxazole-4-propionate antagonist. In sep. exptl. groups, L-trans-PDC-evoked glutamate levels were reduced significantly by 55% in the presence of 0.1 mM calcium and by 46% in the presence of tetrodotoxin. Addnl., CPP and LY293558 significantly attenuated L-trans-PDC-evoked glutamate levels without altering basal glutamate levels. These data suggest that glutamate transporter reversal by L-trans-PDC initially elevates extracellular glutamate levels enough to stimulate postsynaptic glutamate receptors within the striatum. It is proposed that glutamate-receptor stimulation activates a pos. feedback loop within the basal ganglia, leading to further glutamate release from corticostriatal and thalamostriatal afferents. Therefore, either extracellular striatal calcium reduction or tetrodotoxin perfusion leads to decreased action potential-dependent glutamate release from these terminals. In addition, blocking glutamate receptors directly reduces medium spiny neuronal firing and indirectly attenuates corticostriatal and thalamostriatal activity, resulting in an overall depression of L-trans-PDC-stimulated glutamate levels.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pyrrolidinedicarboxylate-evoked striatal glutamate levels are attenuated by calcium reduction, tetrodotoxin, and glutamate receptor blockade)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).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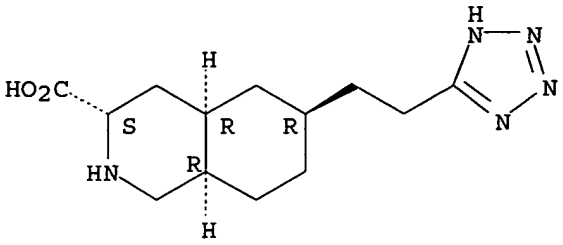
L4 ANSWER 49 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:181183 CA
TITLE: A selective AMPA antagonist, LY293558, suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal
AUTHOR(S): Rasmussen, Kurt; Kendrick, William T.; Kogan, Jeffrey H.; Aghajanian, George K.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Neuropsychopharmacology (**1996**), 15(5), 497-505
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The glutamate receptor subtype that mediates the morphine withdrawal-induced activation of locus coeruleus (LC) neurons was examined in this study using in vitro and in vivo single-unit electrophysiol. recordings. For LC neurons recorded in vitro in rat brain slices, the selective α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonist, LY293558, showed a greater than 10-fold selectivity for inhibiting the excitatory effects of AMPA vs. kainate, and a greater than 30-fold selectivity for inhibiting the excitatory effects of AMPA vs. NMDA. LY293558 also greatly reduced the response of LC neurons to glutamate in a concentration-dependent manner. In in vivo recordings in anesthetized rats, pretreatment with LY293558 (0.1 to 10 mg/kg, IP) dose dependently suppressed the morphine withdrawal-induced activation of LC neurons. In unanesthetized, morphine-dependent animals, pretreatment with LY293558 (1 to 30 mg/kg, IP) dose dependently suppressed naltrexone-precipitated morphine withdrawal signs. These results indicate: (1) AMPA receptors mediate a large component of the excitatory effects of glutamate on LC neurons; (2) activation of AMPA receptors plays an important role in the morphine withdrawal-induced activation of LC neurons; (3) AMPA antagonists can suppress many signs of morphine withdrawal in awake animals; and (4) AMPA antagonists may have therapeutic effects in humans for the treatment of opiate withdrawal.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA antagonist LY293558 suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).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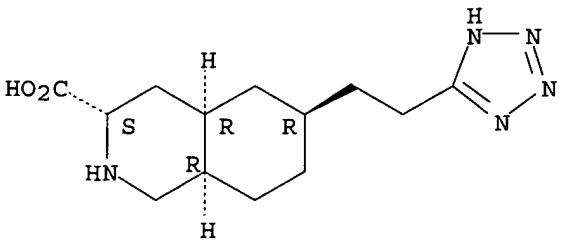
L4 ANSWER 50 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:99235 CA
TITLE: Disruption of learning by excitatory amino acid receptor antagonists
AUTHOR(S): Baron, S. P.; Moerschbaecher, J. M.
CORPORATE SOURCE: Medical Center, Louisiana State University, New Orleans, LA, 70112, USA
SOURCE: Behavioural Pharmacology (**1996**), 7(6), 573-584
CODEN: BPHAEL; ISSN: 0955-8810
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Compds. that act as competitive or uncompetitive N-methyl-D-aspartate (NMDA) antagonists, glycine/NMDA-site antagonists, or α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxalzolepropionic acid (AMPA)-receptor antagonists were evaluated for effects on a repeated acquisition of behavioral chains schedule by rats. Responding by rats was maintained by food presentation under a repeated acquisition or a performance procedure. Under the repeated acquisition procedure, subjects acquired a different three-response chain each daily session. Thus, each day a new learning curve could be generated for each animal thereby providing a repeated measure of learning. Food was presented under a second-order fixed-ratio three (FR3) schedule. Under the performance schedule rats responded under the same second-order FR3 schedule of food presentation: however, instead of a new sequence being presented each day, the same sequence of responding was required for each daily session. Both the competitive (CGS 19755) and uncompetitive (dizocilpine) NMDA antagonists disrupted repeated acquisition at doses that did not disrupt performance. In contrast, the glycine/NMDA antagonist MDL 104,653 or the competitive AMPA receptor antagonist LY 293558 did not disrupt acquisition or performance up to doses that suppressed responding. These results suggest there are different roles for various excitatory amino acid receptors, or sites on the NMDA receptor, in the neural bases of learning and that the disruption of acquisition by glutamate antagonists is dependent upon the particular receptor at which they have activity as well as the particular modulatory site of action.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(disruption of learning by excitatory amino acid receptor antagonists in rats)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

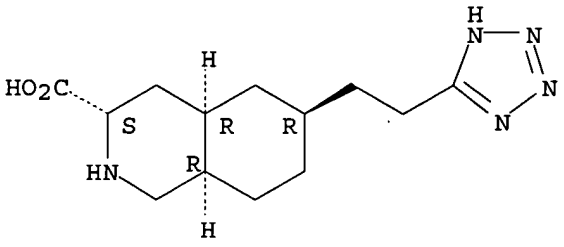
L4 ANSWER 51 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:75197 CA
TITLE: Synthesis and characterization of phosphonic acid-substituted amino acids as excitatory amino acid receptor antagonists
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Allen, Nancy K.; Schoepp, Darryle D.
CORPORATE SOURCE: Central Nervous System Res. Div., A Div. Eli Lilly Co., Indianapolis, IN, 46285, USA
SOURCE: Phosphorus, Sulfur and Silicon and the Related Elements (**1996**), 109-110(1-4, Proceedings of the Thirteenth International Conference on Phosphorus Chemistry, 1995), 309-312
CODEN: PSSLEC; ISSN: 1042-6507
PUBLISHER: Gordon & Breach
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Decahydroisoquinoline-3-carboxylic acids, substituted at C-6 with an acidic moiety such as a phosphonic, sulfonic or carboxylic acid or tetrazole, were prepared as antagonists of excitatory amino acid (EAA) receptors.

IT **154652-83-2P**, Ly293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and characterization of phosphonic acid-substituted amino acids as excitatory amino acid receptor antagonists)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

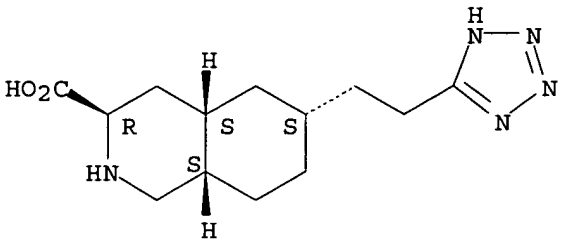


L4 ANSWER 52 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:1010 CA
TITLE: Selective protection against AMPA- and kainate-evoked neurotoxicity by (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558) and its racemate (LY215490)
AUTHOR(S): Schoepp, D. D.; Salhoff, C. R.; Fuson, K. S.; Sacaan, A. I.; Tizzano, J. P.; Ornstein, P. L.; May, P. C.
CORPORATE SOURCE: Lilly Research Labs., Eli Lilly Co., Indianapolis, IN, USA
SOURCE: Journal of Neural Transmission (**1996**), 103(8-9), 905-916
CODEN: JNTRF3; ISSN: 0300-9564
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamate receptor-mediated excitotoxicity is linked to the activation of multiple receptors including those activated by α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. In this study, the novel glutamate receptor antagonist, as its active isomer (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid ((-)LY293558) and it's ± racemate (LY215490), was examined for neuroprotectant effects against excitotoxic injury in vitro and in vivo. This agent selectively protected against AMPA and kainate injury in cultured primary rat hippocampal neurons, an in vivo rat striatal neurotoxicity model, and against agonist-evoked seizures in mice. Thus, (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid represents a novel receptor selective and potent systemically active AMPA/kainate receptor antagonist for exploring neuroprotection via non-NMDA receptor mechanisms.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(LY293558 and LY215490 in neuroprotection against AMPA- and kainate-evoked neurotoxicity)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



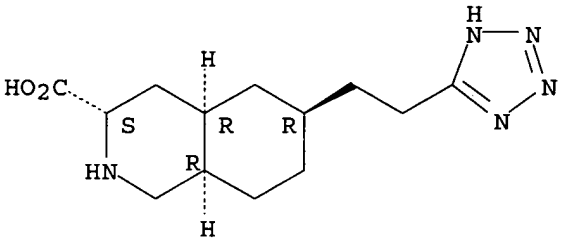
L4 ANSWER 53 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 125:238444 CA
TITLE: The AMPA antagonist LY293558 improves functional neurological outcome following reversible spinal cord ischemia in rabbits
AUTHOR(S): Bowes, Mark P.; Swanson, Steven; Zivin, Justin A.
CORPORATE SOURCE: School Medicine, University California, La Jolla, CA, 92093-0624, USA
SOURCE: Journal of Cerebral Blood Flow and Metabolism (**1996**), 16(5), 967-972
CODEN: JCBMDN; ISSN: 0271-678X
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamate (Glu) neurotoxicity is an important element of a number of neurol. disorders including central nervous system (CNS) ischemia. We evaluated the effects of the novel AMPA Glu antagonist LY293558 on functional neurol. outcome in two rabbit stroke models. In the reversible spinal cord ischemia model, ischemia of the caudal lumbar spinal cord was produced by temporary occlusion of the abdominal aorta. LY293558 was administered 5 min after recirculation as a 16 mg/kg i.v. bolus followed by 2.2 mg/kg infused over 1 h. Control animals received saline. LY293558 significantly increased the duration of ischemia required to produce paraplegia, from 30.5 ± 15.8 min (mean ± SD) controls to 50.1 ± 11.5 in treated animals ($p < 0.01$). In an irreversible model of cerebral ischemia, 50 μm plastic microspheres were injected into the carotid artery and lodged in the cerebral microvasculature. LY293558 did not significantly reduce neurol. damage in this model. These data suggest that LY293558 may have therapeutic benefit following some types of ischemic injury.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AMPA antagonist LY293558 improves functional neurol. outcome following reversible spinal cord ischemia)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



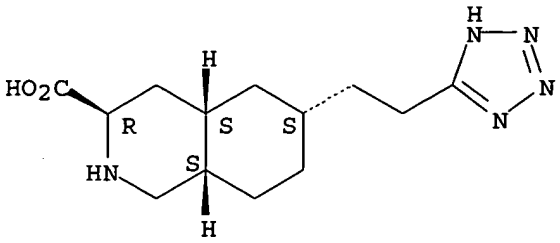
L4 ANSWER 54 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 125:320 CA
TITLE: Structure-Activity Studies of 6-Substituted Decahydroisoquinoline-3-carboxylic Acid AMPA Receptor Antagonists. 2. Effects of Distal Acid Bioisosteric Substitution, Absolute Stereochemical Preferences, and in Vivo Activity
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Allen, Nancy K.; Bleisch, Thomas; Borromeo, Peter S.; Lugar, Charles W.; Leander, J. David; Lodge, David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (**1996**), 39(11), 2232-44
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have explored the excitatory amino acid antagonist activity in a series of decahydroisoquinoline-3-carboxylic acids, and within this series found the potent and selective AMPA antagonist (3SR,4aRS,6RS,8aRS)-6-[2-(1H-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (I). In this and the preceding paper, we looked at the structure-activity relationships for AMPA antagonist activity in this series of compds. We have already shown that I had the optimal stereochem. array and that AMPA antagonist activity was maximized for a two-carbon spacer separating a tetrazole from the bicyclic nucleus. In this paper, we explored the effects of varying the distal acid and the absolute stereochem. preferences of many of these analogs. We looked at a variety of different acid bioisosteres, including 5-membered hetereocyclic acids such as tetrazole, 1,2,4-triazole, and 3-isoxazolone; carboxylic, phosphonic, and sulfonic acid; and acyl sulfonamides. Compds. were evaluated in rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([3H]AMPA), NMDA ([3H]CGS 19755), and kainic acid ([3H]kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 μM), NMDA (40 μM), and kainic acid (10 μM). A number of compds. from this and the preceding paper were also evaluated in mice for their ability to block maximal electroshock-induced convulsions and ATPA-induced rigidity in mice.

IT **150131-79-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(decahydroisoquinolinecarboxylic acid AMPA antagonists: effects of distal acid bioisosteric substitution, absolute stereochem. preferences, and activity)

RN 150131-79-6 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

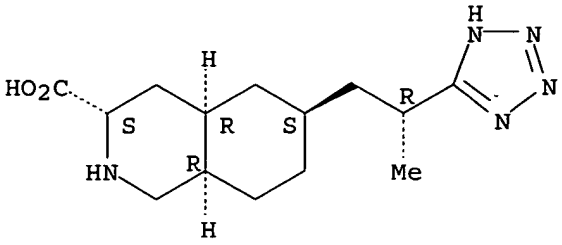


L4 ANSWER 55 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 125:319 CA
TITLE: Structure-Activity Studies of 6-(Tetrazolylalkyl)-Substituted Decahydroisoquinoline-3-carboxylic Acid AMPA Receptor Antagonists. 1. Effects of Stereochemistry, Chain Length, and Chain Substitution
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Allen, Nancy K.; Bleisch, Thomas; Borromeo, Peter S.; Lugar, Charles W.; Leander, J. David; Lodge, David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (**1996**), 39(11), 2219-31
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of 6-substituted decahydroisoquinoline-3-carboxylic acids were prepared as excitatory amino acid (EAA) receptor antagonists. These compds. are antagonists at the N-methyl-D-aspartate (NMDA) and 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) subclasses of ligand gated ion channel (ionotropic) EAA receptors. (3S,4aR,6R,8aR)-6-(2-(1H-tetrazol-5-yl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (I) is a potent, selective and systemically active AMPA antagonist. Other analogs from this series, including (3S,4aR,6S,8aR)-6-((1H-tetrazol-5-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (II) and (3S,4aR,6S,8aR)-6-(phosphonomethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (III) are potent, selective, and systemically active NMDA antagonists. The authors report the effects of varying stereochem. around the hydroisoquinoline ring; of tetrahydro- vs. decahydroisoquinoline; of having the carboxylic acid at C-1 vs. C-3; of varying the length of the carbon chain connecting a tetrazole to the bicyclic nucleus; and of holding the connecting chain constant at two atoms, the effect of heteroatom substitution in the position adjacent to the bicyclic nucleus and substitution with Me or Ph on the chain. Compds. were evaluated on rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([3H]AMPA), NMDA ([3H]CGS 19755), and kainic acid ([3H]kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 μM), NMDA (40 μM), and kainic acid (10 μM). The optimal stereochem. array was the same for both NMDA (II and III) and AMPA (I) antagonists identified in this series and that the tetrahydroisoquinoline and the C-1 carboxy analogs of I are inactive. With a tetrazole in the distal acid position, an ethylene spacer is optimal; substitution with oxygen or nitrogen on the chain in the position adjacent to the bicyclic nucleus significantly reduced activity, while substitution with a Me or Ph group on the chain was well tolerated.

IT **177098-81-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity studies of (tetrazolylalkyldecahydroisoquinolinecarboxylates as AMPA receptor antagonists)
RN 177098-81-6 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)propyl]-, [3α,4aα,6β(S*),8aα]- (9CI) (CA INDEX NAME)

Relative stereochemistry.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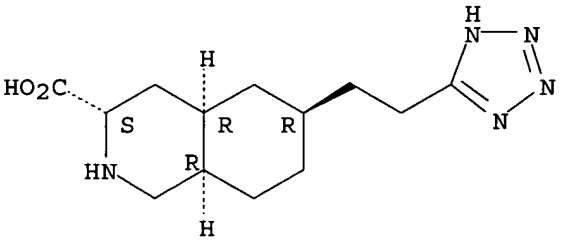
L4 ANSWER 56 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 124:307404 CA
TITLE: Pharmacological discrimination of GluR5 and GluR6 kainate receptor subtypes by (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic-acid
AUTHOR(S): Bleakman, David; Schoepp, Darryle D.; Ballyk, Barbara; Bufton, Hywel; Sharpe, Erica F.; Thomas, Kathy; Ornstein, Paul L.; Kamboj, Rajender K.
CORPORATE SOURCE: Eli Lilly and Company, Lilly Research Centre, Windlesham, Surrey, GU20 6PH, UK
SOURCE: Molecular Pharmacology (**1996**), 49(4), 581-5
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacol. tools available for the discrimination of kainate receptor subtypes are limited. The authors examined the effects of (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558) and 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX) on inward currents associated with activation of non-N-methyl-D-aspartate (NMDA) receptors in acutely isolated rat cerebellar Purkinje neurons, rat dorsal root ganglion neurons, and human embryonic kidney 293 cells transfected with human glutamate receptors (GluR) 5 and 6. LY293558 and NBQX inhibited kainate-induced currents in cerebellar Purkinje cells, dorsal root ganglion (DRG) neurons, and human GluR5-transfected cells. In contrast, human embryonic kidney 293 cells expressing GluR6 receptors, although blocked by NBQX, were unaffected by LY293558 at concns. of ≤100 μM. The selective antagonism by LY293558 of GluR5 receptors should allow the determination of the functional role of GluR5 and GluR6 in more complex systems.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. discrimination of GluR5 and GluR6 kainate receptor subtypes by [(tetrazoleyl)ethyl]decahydroisoquinolinecarboxylic acid)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 57 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 124:106393 CA
TITLE: Effects of decahydroisoquinoline-3-carboxylic acid monohydrate, a novel AMPA receptor antagonist, on glutamate-induced Ca2+ responses and neurotoxicity in rat cortical and cerebellar granule neurons
AUTHOR(S): Liljequist, Sture; Cebers, Gvido; Kalda, Anti
CORPORATE SOURCE: Department Clinical Neuroscience, Karolinska Institute, Stockholm, S-17176, Swed.
SOURCE: Biochemical Pharmacology (**1995**), 50(11), 1761-74
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, we examined the effects of a novel water-soluble, putative AMPA receptor antagonist, (-)(3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid monohydrate (LY326325), on glutamate-, N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-, and kainic acid (KA)-induced elevations of intracellular Ca2+ concns. ([Ca2+]i) and 45Ca2+ uptake, as well as glutamate agonist-induced neurotoxicity in primary cultures of intact rat cortical and cerebellar granule neurons. In some expts., the actions of LY326325 were tested in the presence of cyclothiazide, a compound that is known to block glutamate-induced desensitization of AMPA-preferring subtypes of glutamate receptors, thereby largely potentiating the functional effects of AMPA. LY326325 fully blocked the elevations of [Ca2+]i induced by NMDA and non-NMDA glutamate receptor agonists in both cortical and cerebellar granule neurons. The application of increasing concns. of cyclothiazilde was not able to reverse the LY326325-induced blockade of glutamate receptors in cortical neurons. In contrast, the same cyclothiazide treatment fully reversed the blockade produced by the noncompetitive AMPA/KA receptor antagonist 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine HCl (GYKI 52466). In 45Ca2+ uptake studies. LY325325 inhibited the NMDA-, AMPA-, and KA-induced enhancement of 45Ca2+ uptake in a concentration-dependent fashion in both cortical and cerebellar granule cells. In analogy to the results obtained with [Ca2+]i recordings, cyclothiazide failed to counteract the LY326325-induced blockade of KA-stimulated 45Ca2+ uptake in cerebellar granule neurons, whereas the blockade induced by the noncompetitive AMPA/KA receptor blocking agent GYKI 52466 was fully reversed by cyclothiazide. Because a similar, although no identical pattern of actions was seen following the application of the competitive AMPA/KA receptor antagonist 6-nitro-7-sulphamoyl-benzo(f)quinoxaline-2-3-dione (NBQX), it is suggested that the inhibitory actions of LY326325 are similar to those produced by NBQX but clearly differ from those caused by the noncompetitive AMPA/KA receptor antagonist GYKI 52466. Finally, when the neuroprotective actions of LY326325 on glutamate agonist-induced neurotoxicity were examined in cerebellar granule neurons, we found that LY326325 almost completely blocked the neurotoxic actions of NMDA, AmPA, and KA, resp., whereas it produced only a partial blockade of glutamate-induced neurotoxicity. Taken together, our current results suggest that although LY326325 blocked both nonNMDA and NMDA-induced Ca2+ responses, it still displayed a preferential affinity for nonNMDA receptors as compared to NMDA receptors. However, LY326325 appears to be a less selective AMPA/KA receptor antagonist than NBQX and GYKI52466, resp.

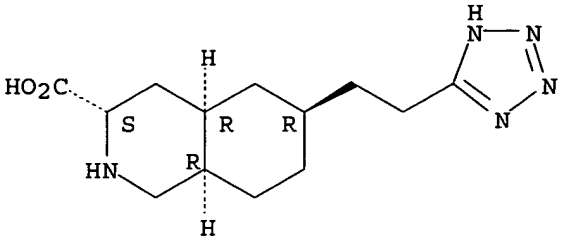
IT **154652-83-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of AMPA receptor antagonist LY326325 on glutamate-induced Ca2+ responses and neurotoxicity in rat cortical and cerebellar granule neurons)

RN 154652-83-2 CA

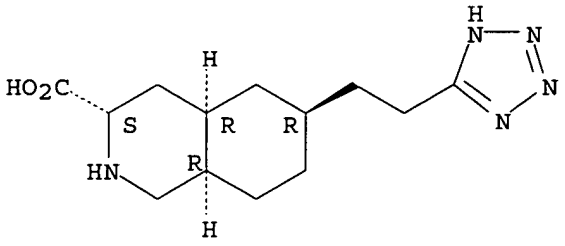
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 58 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 124:45454 CA
TITLE: AMPA antagonist LY293558 does not affect the severity of hypoxic-ischemic injury in newborn pigs
AUTHOR(S): LeBlanc, Michael H.; Li, Xin Qin; Huang, Min; Patel, Daksha M.; Smith, Edward E.
CORPORATE SOURCE: Medical Center, University Mississippi, Jackson, MS, 39216-4505, USA
SOURCE: Stroke (Dallas) (**1995**), 26(10), 1908-15
CODEN: SJCCA7; ISSN: 0039-2499
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The systemically active AMPA antagonist LY293558, when given at 5 mg/kg or 15 mg/kg before injury and 10 h later, did not affect the severity of hypoxic-ischemic brain injury in newborn piglets.
IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA antagonist LY 293558 does not affect brain ischemia in newborn)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

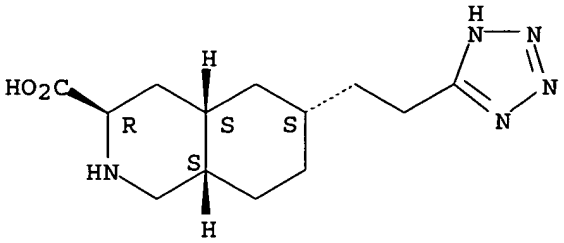


L4 ANSWER 59 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 123:329860 CA
TITLE: Schedule-controlled behavioral effects of the selective 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid antagonist LY293558 in pigeons
AUTHOR(S): Benvenga, Mark J.; Ornstein,. Paul L.; Leander, J. David
CORPORATE SOURCE: Lilly Res. Labs., Lilly Corporate Center, Eli Lilly & Company, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1995**), 275(1), 164-70
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Behavioral effects of the selective 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) antagonist LY293558, along with its racemate (LY215490) and opposing enantiomer (LY293559) were evaluated in pigeons. When responding was maintained under a multiple fixed ratio 50 responses, fixed interval 5 min (FRFI) schedule of food presentation, LY215490 completely antagonized the rate suppression induced by AMPA (10 mg/kg) and by the AMPA analog, 2-amino-3-hydroxy-5-tert-butyl-4-isoxazolepropionic acid (ATPA; 40 mg/kg) at 1.25 and 2.5 mg/kg, resp. In contrast, LY215490, up to 10 mg/kg, was unable to antagonize the rate suppression induced by N-methyl-D-aspartic acid. LY293558, at 0.32 mg/kg, completely blocked the rate suppression produced by AMPA in both components of the multiple schedule. Similarly, LY293558, at 0.64 mg/kg, blocked the rate suppression induced by ATPA in both components. In contrast, the opposing enantiomer, LY293559, up to 10 mg/kg, was without effect on rate suppression produced by AMPA in this model. In addnl. studies, behavior was maintained under a schedule in which responding was maintained by food presentation in the presence of one key color and in the presence of a second key color, responding was maintained by food and simultaneously suppressed by elec. shock ("punished responding"). LY215490 significantly increased punished responding at 10 and 30 mg/kg, whereas unpunished responding was unaffected until 56 mg/kg depressed it. LY293558 significantly increased punished responding at 3 mg/kg without having an effect on unpunished responding. The results of these expts. suggest that LY293558 is an antagonist at those glutamate receptors activated by AMPA. Addnl., those compds. that act as antagonists at the AMPA subtype of glutamate receptor produce increases in punished responding in pigeons.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(schedule-controlled behavioral effects of the selective 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid antagonist LY293558 in pigeons)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.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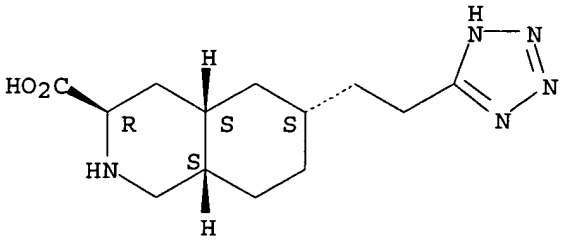
L4 ANSWER 60 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 123:246679 CA
TITLE: In vitro and in vivo antagonism of AMPA receptor activation by (3S,4aR,5R,8aR)-6-[2-(1(2H)-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid
AUTHOR(S): Schoepp, D. D.; Lodge, D.; Bleakman, D.; Leander, J. D.; Tizzano, J. P.; Wright, R. A.; Palmer, A. J.; Salhoff, C. R.; Ornstein, P. L.
CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Neuropharmacology (**1995**), 34(9), 1159-68
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro and in vivo pharmacol. of a structurally novel competitive antagonist for the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype of excitatory amino acid receptors is described. LY215490, (±)(6-(2-(1-H-tetrazol-5-yl)ethyl)decahydroisoquinoline-3-carboxylic acid), was shown to displace selectively 3H-AMPA and 3H-6-cyano-y-nitro-quinoxaline-2,3-dione (3H-CNQX) binding to rat brain membranes. LY215490 potently antagonized quisqualate-and AMPA-induced depolarization of rat cortical slices in a competitive manner, while requiring higher concns. to antagonize the effects of N-methyl-D-aspartate (NMDA) and kainate. In slices of rat hippocampus, LY215490 also selectively antagonized AMPA-evoked release of 3H-norepinephrine. These AMPA receptor activities were due to the (-) isomer of the compound, (3S,4aR,6R,8aR)-6-[2-(1(2-H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558). LY215490 was centrally active following parenteral administration in mice as demonstrated by protection vs. maximal electroshock seizures and decreases in spontaneous motor activity. LY215490 (its active isomer being LY293558) represents a novel pharmacol. agent for in vitro and in vivo studies of AMPA receptor function in the CNS.

IT **150010-68-7**, LY215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(antagonism of brain AMPA receptor activation by tetrazoleylethyldecahydroisoquinolinecarboxylic acid)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



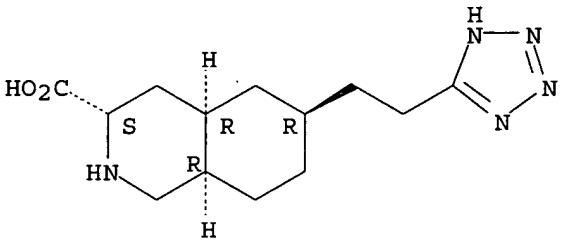
L4 ANSWER 61 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 123:47726 CA
TITLE: Evidence for an anxiogenic action of AMPA receptor antagonists in the plus-maze test
AUTHOR(S): Karcz-Kubicha, Marzena; Liljequist, Sture
CORPORATE SOURCE: Department of Clinical Neuroscience, Division of Drug Dependence Research, Karolinska Hospital, Stockholm, S-17176, Swed.
SOURCE: European Journal of Pharmacology (**1995**), 279(2/3), 171-7
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the non-NMDA receptor antagonists, the new α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-selective receptor antagonist, LY326325, and the AMPA/kainate-selective receptor antagonist, NBQX (6-nitro-7-sulfamoylbenzo(f)quinoxaline-2,3-(1H,4H)dione), on plus-maze behavior and locomotor activity were examined LY326325 induced a dose-dependent decrease in the per cent time spent in open arms as well as in the per cent entries into the open arms. NBQX caused a dose-dependent reduction in the per cent time spent in open arms but had no effect on the per cent entries into the open arms. The behavioral actions of the AMPA receptor antagonists were observed at doses which had no influence on the locomotor activity of the animals. Based upon the current findings it is suggested that AMPA receptor antagonists produce a dose-dependent increase of anxiogenic behavior in the plus-maze test situation.

IT **154652-83-2**, LY 293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(anxiogenic action of AMPA receptor antagonists in the plus-maze test)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

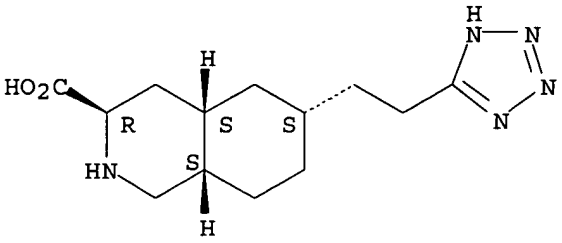


L4 ANSWER 62 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:151230 CA
TITLE: The neuroprotective effects of the decahydroisoquinoline, LY 215490; a novel AMPA antagonist in focal ischemia
AUTHOR(S): Gill, R.; Lodge, D.
CORPORATE SOURCE: R. Vet. Coll., Dep. Vet. Basic Sci., London, NW1 0TU, UK
SOURCE: Neuropharmacology (**1994**), 33(12), 1529-36
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY 215490 (3RS,4aRS,6RS,8aRS-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid), a novel, selective, competitive and systemically active AMPA receptor antagonist was tested as a neuroprotective agent against focal ischemia in a model of permanent MCA occlusion in the rat. LY 215490 was administered at a dose of 10, 30 or 100 mg/kg 30 min prior to and post-MCA occlusion. The animals were allowed to survive for 24 h, following which time the brains were processed for volumetric anal. of the infarct size. The low dose of LY 215490 was not effective against the infarct volume in the hemisphere, cortex or caudate. The 2 + 30 mg/kg dose of LY 215490 resulted in 25 and 31% protection against the volume of hemispheric and cortical ischemic damage, resp. The highest dose of LY 215490 resulted in a reduced neuroprotective effect with 23 and 27% protection against the volume of hemispheric and cortical ischemic damage, resp. The slightly reduced neuroprotective effect of the highest dosing regimen may be due to the respiratory problems seen with this dose. Neither of the two neuroprotective doses of LY 215490 produced any reduction in the volume of caudate damage which represents the core of the infarct.

IT **150010-68-7**, LY 215490
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(decahydroisoquinoline LY 215490 neuroprotective activity in focal brain ischemia)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



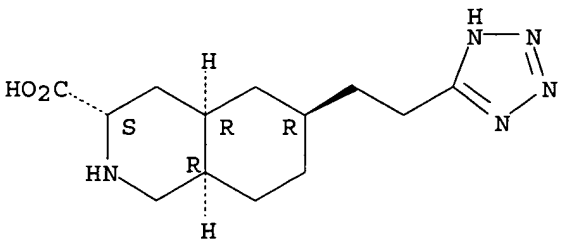
L4 ANSWER 63 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:96281 CA
TITLE: Cyclothiazide acts at a site on the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor complex that does not recognize competitive or noncompetitive AMPA receptor antagonists
AUTHOR(S): Desai, Manisha A.; Burnett, J. Paul; Ornstein, Paul L.; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1995**), 272(1), 38-43
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype of ionotropic glutamate receptors by certain agonists, including AMPA and glutamate, has been shown to result in a rapid desensitization of the receptor. This desensitization is profoundly inhibited by the benzothiadiazoide diuretic, cyclothiazide. The authors previously reported that cyclothiazide potentiates AMPA-induced [3H]norepinephrine ([3H]NE) release from rat hippocampal slices. The authors used this system to investigate the possible interaction of cyclothiazide with various AMPA receptor antagonists, including the competitive antagonist LY293558 and the 2,3-benzodiazepine noncompetitive antagonist GYKI 53655. Cyclothiazide significantly potentiated both AMPA- and kainic acid (KA)-induced [3H]NE release from slices of the rat hippocampus. LY293558 and GYKI 53655 inhibited the potentiated and nonpotentiated AMPA- and KA-induced [3H]NE release in a concentration-dependent manner. The IC50 values for inhibition of AMPA- or KA-induced [3H]NE release by either antagonist were not affected by the presence of cyclothiazide. Thus, cyclothiazide seems to interact at a site on the AMPA receptor complex which differs from either the glutamate recognition site or the 2,3-benzodiazepine allosteric site.

IT **154652-83-2**, LY293558
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclothiazide acts at site on aminohydroxymethylisoxazole propionic acid (AMPA) receptor complex that does not recognize competitive or noncompetitive AMPA receptor antagonists)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 64 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:81140 CA
TITLE: Excitatory amino acid receptor antagonists
INVENTOR(S): Huff, Bret
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: U.S., 44 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 5284957	A	19940208	US 1992-939780	19920903	<--
EP 590789	A1	19940406	EP 1993-306745	19930825	<--
EP 590789	B1	20030312			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
ZA 9306231	A	19950227	ZA 1993-6231	19930825	<--
US 5399696	A	19950321	US 1993-111747	19930825	<--
CZ 285049	B6	19990512	CZ 1993-1745	19930825	<--
AT 234287	E	20030315	AT 1993-306745	19930825	
PT 590789	T	20030731	PT 1993-306745	19930825	
ES 2194844	T3	20031201	ES 1993-306745	19930825	
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IL 106809	A1	19990312	IL 1993-106809	19930826	<--
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AU 9346003	A1	19940310	AU 1993-46003	19930831	<--
AU 656482	B2	19950202			
RU 2117661	C1	19980820	RU 1993-49265	19930831	<--
JP 06199802	A2	19940719	JP 1993-217441	19930901	<--
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US 5637712	A	19970610	US 1994-343079	19941121	<--
US 5606062	A	19970225	US 1995-457556	19950601	<--
US 5648492	A	19970715	US 1995-456577	19950601	<--
US 5670516	A	19970923	US 1995-456439	19950601	<--
US 5675008	A	19971007	US 1995-457766	19950601	<--
HK 1013989	A1	20031224	HK 1998-115176	19981223	

PRIORITY APPLN. INFO.:		
US 1992-939780	A	19920903
US 1993-111747	A3	19930825
CA 1993-2104909	A3	19930826
US 1994-343079	A3	19941121

OTHER SOURCE(S): MARPAT 122:81140
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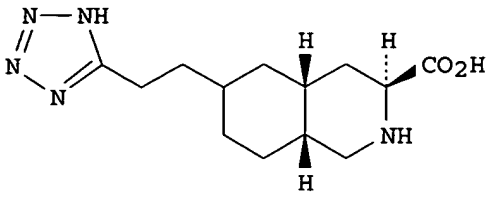


I

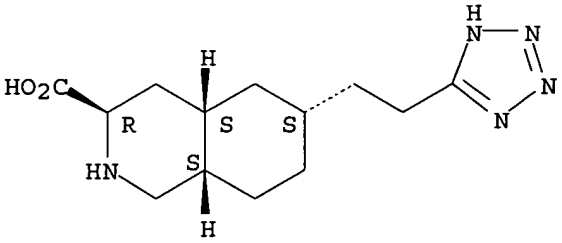
AB This invention provides compds. which are useful in the preparation of AMPA receptor antagonists. Such AMPA receptor antagonists are racemic compds. such as the [(tetrazolyl)alkyl]octahydroizoquinolinecarboxylic acid I.

IT **150010-68-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as AMPA antagonist)

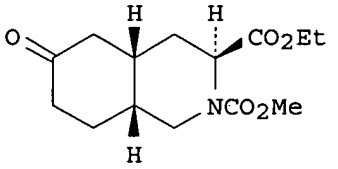
RN 150010-68-7 CA

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 65 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:10520 CA
TITLE: Stereoselective Synthesis of 6-Substituted Decahydroisoquinoline-3-carboxylates: Intermediates for the Preparation of Conformationally Constrained Acidic Amino Acids
AUTHOR(S): Ornstein, Paul L.; Augenstein, Nancy K.; Arnold, M. Brian
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Organic Chemistry (**1994**), 59(25), 7862-9
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 122:10520
GI



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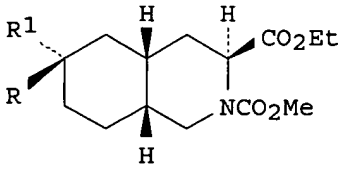
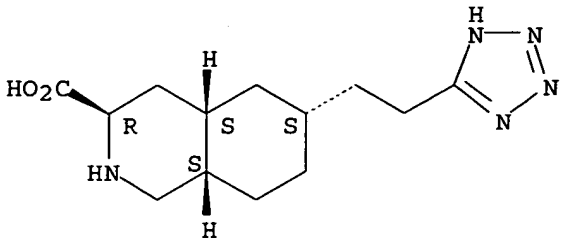


II

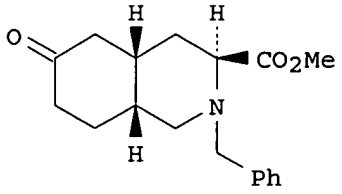
AB The stereoselective preparation of two 6-(hydroxymethyl) substituted decahydroisoquinoline-3-carboxylates, which are useful in the synthesis of a number of excitatory amino acid antagonists, e.g. LY235959, LY202157, and LY293558, is described. Thus, the known ketone I was converted to either the racemic alc. II (R = H, R1 = CH2OH) or racemic alc. II (R = CH2OH, R1 = H), the former via a stereoselective hydroboration reaction, the latter via a stereoselective enol ether hydrolysis followed by reduction Epimeric alcs. II were easily converted to a number of useful intermediates, e.g., aldehydes, bromides and iodides. If resolved ketone I were used, these intermediates could be obtained in optically active form. In either racemic or non-racemic form, these intermediates provided access to a number of diastereomerically pure amino acids that were difficult to obtain by earlier routes.

IT **150010-68-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereoselective synthesis of substituted decahydroisoquinolinecarboxyl ates as intermediates in the preparation of conformationally constrained acidic amino acids)
RN 150010-68-7 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 66 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:300735 CA
TITLE: intramolecular Diels-Alder route to 6-oxodecahydroisoquinoline-3-carboxylates: intermediates for the synthesis of conformationally constrained excitatory amino acid antagonists
AUTHOR(S): Ornstein, Paul L.; Melikian, Anita; Martinelli, Michael J.
CORPORATE SOURCE: Lilly Res. Lab., Lilly Corp. Cent., Indianapolis, IN, 46285, USA
SOURCE: Tetrahedron Letters (**1994**), 35(32), 5759-62
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



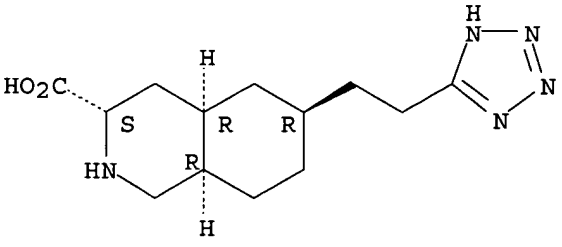
I

AB The preparation of a hydroisoquinoline intermediate potentially useful for the synthesis of some excitatory amino acid antagonists was reported. The requisite stereochem. is established by an intramol. Diels-Alder reaction, and the absolute stereochem. is ultimately derived from S-aspartic acid. Also reported is an efficient synthesis of Me N-CBZ aspartate β-aldehyde. The 6-oxodecahydro-3-isoquinolinecarboxylate I was prepared

IT **154652-83-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of decahydro(oxo)-3-quinolinecarboxylate intermediate via Diels-Alder reaction)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

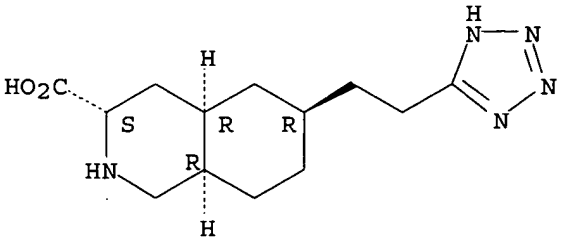


L4 ANSWER 67 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:125011 CA
TITLE: Neuroprotective effect of the AMPA receptor antagonist LY-293558 in focal cerebral ischemia in the cat
AUTHOR(S): Bullock, R.; Graham, D. I.; Swanson, S.; McCulloch, J.
CORPORATE SOURCE: Wellcome Surg. Inst. and Hugh Fraser Neurosci. Lab., Univ. Glasgow, Glasgow/Scotland, G61 1QH, UK
SOURCE: Journal of Cerebral Blood Flow and Metabolism (**1994**), 14(3), 466-71
CODEN: JCBMDN; ISSN: 0271-678X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the glutamate α-amino-3-hydroxy 5-methyl-4-isoxazole propionate (AMPA) receptor antagonist LY-293558 in reducing ischemic brain damage have been assessed in halothane-anesthetized cats. Focal cerebral ischemia was produced by permanent occlusion of one middle cerebral artery, and the animals were killed 6 h later. The amount of early irreversible ischemic damage was assessed at 16 predetd. stereotactic planes by an observer blinded to treatment paradigm employed. Treatment with LY-293558 (15 mg/kg i.v., plus infusion of 7 mg/kg/h) initiated 30 min prior to middle cerebral artery occlusion reduced significantly ($p < 0.02$) the volume of ischemic damage (from 3,423 ± 212 mm3 of the cerebral hemisphere in vehicle-treated cats to 2,822 ± 569 mm3 in LY-293558-treated cats). The present data demonstrate that an AMPA receptor antagonist can reduce focal ischemic damage in a gyrencephalic species in which key physiol. variables have been controlled and monitored throughout the postischemic period. These data provide addnl. support for the clin. evaluation of AMPA receptor antagonists in focal cerebral ischemia in humans.

IT **154652-83-2**, LY-293558
RL: PRP (Properties)
(neuroprotective effect of, in focal cerebral ischemia)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

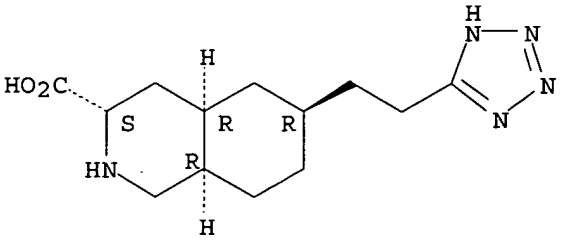


L4 ANSWER 68 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:73642 CA
TITLE: Protection from high pressure induced hyperexcitability by the AMPA/kainate receptor antagonists GYKI 52466 and LY 293558
AUTHOR(S): Pearce, P. C.; Maclean, C. J.; Shergill, H. K.; Ward, E. M.; Halsey, M. J.; Tindley, G.; Pearson, J.; Meldrum, B. S.
CORPORATE SOURCE: Anaesthesia/HPNS Group and Section Med. Statistics, MRC Clinical Res. Centre, Harrow/Middlesex, HA1 3UJ, UK
SOURCE: Neuropharmacology (**1994**), 33(5), 605-12
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neurophysiol. effects of 2 novel AMPA/kainate receptor antagonists, GYKI 52466 and LY 293558, on the high pressure neurol. syndrome have been investigated in the rat and baboon (GYKI 52466) and rat (LY 293558). Rats were exposed to increasing ambient pressures of helium and oxygen at 3 ATA/min, on one occasion each. GYKI 52466 at 20 μmol/kg i.v. immediately before, followed by 70 μmol/kg/h i.v. during compression delayed tremor by 85% and myoclonus by 30%, compared with control vehicle, and no side effects were observed Seizure activity was not affected by any of the doses used. LY 293558 at 36 μmol/kg i.p. delayed tremor and myoclonus (44% and 12%), LY 293558 72 μmol/kg addnl. delayed seizure activity (21%). Side effects, principally tranquilization at the higher dose, were also noted. Six baboons were exposed to a maximum pressure of 91 ATA at 0.3 ATA/min., in the same environment, on two occasions. One exposure was treated with an i.v. infusion of GYKI 52466 15.2 μmol/kg/h, the other with the same volume of control vehicle. Limb and face tremor and myoclonus were delayed and the severity of signs reduced. No seizures were observed in the drug treated group before 91 ATA. EEG changes associated with exposure to pressure were not affected. It is concluded that antagonism at the AMPA/kainate receptor by GYKI 52466 and LY 293558 beneficially alters HPNS signs but in a manner which is dependent on both the drug and species being studied.

IT **154652-83-2**, LY 293558
RL: BIOL (Biological study)
(protection from high pressure induced hyperexcitability by)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



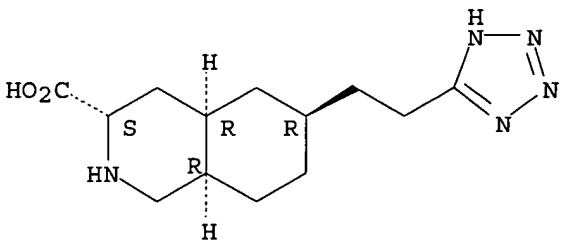
L4 ANSWER 69 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 120:261086 CA
TITLE: AMPA receptor antagonists and local cerebral glucose utilization in the rat
AUTHOR(S): Browne, S. E.; McCulloch, J.
CORPORATE SOURCE: Wellcome Surgical Institute and Hugh Fraser Neuroscience Labs., University of Glasgow, Garscube Estate, Bearsden Road, Glasgow, G61 1QH, UK
SOURCE: Brain Research (**1994**), 641(1), 10-20
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Local cerebral glucose utilization was examined using [14C]2-deoxyglucose autoradiog. following systemic administration of the AMPA antagonists 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX) and 6-(2-(1H-tetrazol-5-yl)ethyl)decahydroisoquinoline-3-carboxylic acid (LY-293558) in conscious rats. Both NBQX (10, 30 and 100 mg/kg) and LY-293558 (10, 30 and 100 mg/kg) produced marked, anatomically widespread, dose-dependent redns. in glucose utilization throughout the brain. In none of the 50 regions investigated were elevations in glucose use observed at any dose of either agent. The redns. in glucose use were accompanied by sedation, suppression of spontaneous behavior, and respiratory depression after NBQX (30 and 100 mg/kg) and LY-293558 (30 and 100 mg/kg) administration. The greatest redns. in glucose use after NBQX or LY-293558 occurred in primary auditory regions, limbic structures (particularly hippocampal regions and cingulate cortex), neocortex and some thalamic nuclei. However, a small number of regions were insensitive to either NBQX or LY-293558, most notably the superior colliculus superficial layer which failed to display significant alterations in glucose use following any concentration of either AMPA antagonist. The anatomical pattern of altered glucose use was essentially similar following either agent although the cerebral cortex, thalamus and auditory regions were more sensitive to LY-293558 and subcortical regions more sensitive to NBQX. The anatomical pattern of glucose use alterations after AMPA receptor antagonists differs from that described previously for competitive and non-competitive NMDA receptor antagonists.

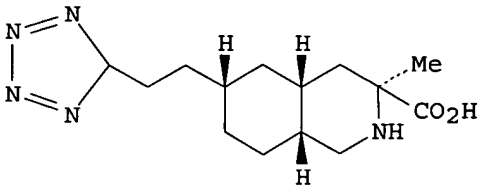
IT **154652-83-2**, LY 293558
RL: BIOL (Biological study)
(glucose metabolism by brain response to, central nervous system depression in relation to)

RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 70 OF 70 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 119:160194 CA
TITLE: (3SR,4aRS,6RS,8aRS)-6-[2-(1H-Tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid: a structurally novel, systemically active, competitive AMPA receptor antagonist
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Augenstein, Nancy K.; Lodge, David; Leander, J. David; Schoepp, Darryle D.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (**1993**), 36(14), 2046-8
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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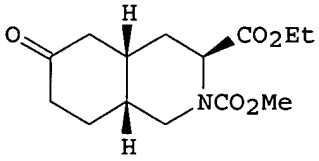
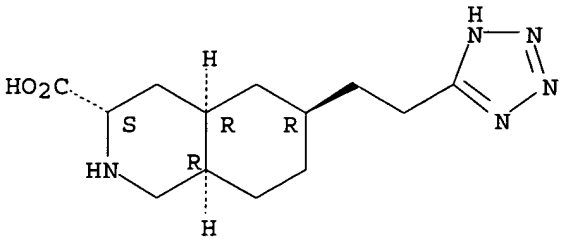


II

AB (±)-, (+)-, And (-)-decahydroisoquinolinecarboxylates I were prepared in 6 steps starting from isoquinolinecarboxylate II via Wittig reaction, oxidation, oxidation by oxalyl chloride, alkylation by (EtO)2P(O)CH2CN, treatment with Mg-MeOH and tetrazole formation by Bu3SnN3. I was an AMPA (2-amino-3-(5-methyl-3-hydroxyisooxazole-4-propanoic acid) competitive antagonist in mice and thus serves as an anticonvulsant.

IT **154652-83-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and anticonvulsant activity of)
RN 154652-83-2 CA
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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L2           37 S L1 FULL

     FILE 'CA' ENTERED AT 13:14:41 ON 08 DEC 2005
L3           85 S L2
L4           70 S L2 AND PY<2003

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---Logging off of STN---


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Executing the logoff script...


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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    331.23     492.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -47.60     -47.60

STN INTERNATIONAL LOGOFF AT 13:15:26 ON 08 DEC 2005
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